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MEDICAL

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 19 1955

TREATMENT OF THYROTOXICOSIS WITH RADIOACTIVE IODINE

REVIEW OF 140 CASES

BY

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It is now thirteen years since Hertz and Roberts (1942) introduced radioactive iodine in the treatment of thyrotoxicosis, and in the succeeding years it has increasingly established itself in the therapy of this condition and has been widely used in the United States of America. We have previously recorded our experience in this country in a small series of cases (Blomfield *et al.*, 1951, 1953; Wayne *et al.*, 1952). Fraser and his colleagues (1954) have also described their results using a somewhat different technique. We have now treated more than 350 patients at Sheffield, and we present a detailed analysis of the results obtained in 140 cases followed up for at least one year. This period of time has been chosen because we found that the full effect of a single dose was obtained within one year. The same rather rigid technique has been used throughout with all the members of this group of patients, and we have aimed at producing a state of normal thyroid balance with a single therapeutic drink of the isotope. We put our results on record because we believe that they will be of interest and value to others who have used different methods to achieve control of the thyrotoxic state.

Selection of Cases

Most observers are now agreed on the main indications for isotope therapy in thyrotoxicosis. The only objection to its wider use is the possible late development of malignant changes in the gland itself. We discuss later the evidence for and against this eventuality. At present we accept the need for caution and we reserve radio-iodine therapy for those with an expectation of life less than that of the latent period for the development of carcinoma, about twenty years. In practice this means that we restrict treatment to the following groups of cases: (*a*) patients over 45 years of age; (*b*) those in whom associated disease reduces life expectancy to less than 20 years; (*c*) those who are refractory or hypersensitive to antithyroid drugs and in whom thyroidectomy is either contraindicated or refused; (*d*) recurrence after thyroidectomy, since antithyroid drug therapy is unlikely to lead to sustained remission and a second operation is much more likely to be followed by further relapse or by some complication; (*e*) cases of heart disease associated with thyrotoxicosis, since expectation of life is low and operative mortality high.

The presence of a large goitre even with chronic pressure symptoms is not in itself a contraindication, as gland shrinkage invariably follows radio-iodine therapy. A toxic adenoma is not an absolute contraindication, and radio-iodine offers a valuable alternative if associated disease seriously militates against surgical treatment.

The only important contraindication is pregnancy. The risk of damage to the foetus as a whole is difficult to estimate but is probably not serious. The risk of the foetal thyroid taking up radio-iodine and receiving direct damage is real. Fortunately this does not occur until after the 14th week of gestation (Chapman *et al.*, 1948), by which time evidence of pregnancy is usually unequivocal.

Dosage and Technique

We have attempted in most cases to deliver to the gland a dose of between 6,000 to 8,000 rads.‡

The cases reported here all had preliminary tracer drinks of radioactive iodine, and from measurements following these we estimated the number of millicuries required to deliver the desired radiation dose. The actual dose delivered was estimated retrospectively from measurements made over seven days following the therapy drink.

The data used for both prediction and retrospective estimation of the dose in this series of cases were: (i) the peak percentage uptake of the isotope by the

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‡1 rad = 100 ergs per gramme of tissue.

gland (U); (ii) the total or effective half-life of the iodine in the gland (T); (iii) the mass of the thyroid (W). In the calculation of the rad dosage (D), the formula $D=\frac{164\times T\times U\times M}{W}$ was used, where M is the number of millicuries in the drink administered.

Of these factors the most difficult to assess is the gland size. In the first twenty cases it was estimated by palpation, but later this was supplemented by physical measurements with a collimated Geiger counter. Measurements were made in two planes, and this enabled a diagram to be constructed of the distribution of activity in the neck so that the mass of the gland could be estimated (Blomfield *et al.*, 1953). The use of the Geiger counter in these measurements, however, required drinks of 100–200 μc., which may have produced biological changes in the gland, since drinks totalling as little as 200 μc. have been shown, especially in children, to have a biological effect (Werner *et al.*, 1952). By using a collimated scintillation counter it is now possible to reduce the drink required for estimation of the size of the gland to 50 μc. An estimate of the biological half-life of the isotope was obtained at the same time.

Procedure

Preliminary radioactive iodine tracer study was usually arranged as an out-patient investigation, and from it the necessary estimates of gland size, peak uptake of radioactive iodine, and effective half-life of the isotope in the gland were obtained.

Thereafter the patient was admitted to hospital, was given a therapeutic drink, and remained in the wards for a further week, during which daily gland counts were carried out. If home conditions permitted she was discharged on the seventh day after therapy. Her subsequent course was supervised at the endocrine clinic, where she attended at monthly intervals for two months, and thereafter, as her progress warranted, at longer intervals.

The assessment of the result was made on clinical grounds. In all doubtful cases, however, the patient was readmitted to hospital for further detailed study. The sleeping pulse rate and the basal metabolic rate were determined, and radioactive iodine diagnostic tests were carried out, the latter being interpreted cautiously after radio-iodine therapy. Post-therapy hypothyroidism was similarly assessed on clinical grounds and further investigated by estimations of serum cholesterol and basal metabolic rate and by electrocardiography. Such cases were photographed and fully reviewed after six weeks' treatment with L-thyroxine sodium.

In those patients whose clinical condition was of such severity as to necessitate rapid control of the thyrotoxic state we used one of the antithyroid drugs. A few days after discontinuing the drug we carried out our procedure as for previously untreated patients.

Results

In all, 140 cases were reviewed; of these 106 were female and 34 male, giving a female:male ratio of 3:1. The average age of the treated cases was 48.9 years.

Table I shows the condition of the thyroid gland of the treated cases, from which it will be seen that the method has been applied to cases of thyrotoxicosis irrespective of the type of gland. The gland types were classified by palpation except in the post-operative group. The largest group had diffuse glandular enlargement (47%), with nodular enlargement next in frequency (20%). In 20 cases (14%) the gland was not enlarged, and in 17 (12%) the disease had recurred after previous thyroidectomy. In 6 cases (4%) a single toxic adenoma was thought to be present; these cases were treated because of the coexistence of cardiac disease or because surgery was refused.

The clinical status of the patients at the time of assessment, and the number of treatments required to give the final clinical result, are shown in Table I. 118 (84%) cases are euthyroid, 87 of which (62% of the total number treated) were successfully cured with one drink. Two drinks were required in 25 (18%) cases, and in 6 (4%) three or more doses were required. It is our practice to allow four to six months to elapse between successive doses, since we have found that improvement may continue over this period of time. Nearly all patients are improved to some extent following a dose of radioactive iodine, so that this delay is relatively unimportant.

Of the 6 cases requiring three or more treatments, 5 required three and 1 required five. The last was a young woman who had a post-operative recurrence which was refractory to methyl thiouracil. She had a very large recurrent diffuse goitre and was extremely ill. She proved relatively resistant also to radioactive iodine and required five doses of the isotope over a period of two years, totalling 70.2 mc. and delivering an estimated 25,000 rads to the gland before she became euthyroid. One patient died from cerebral haemorrhage two days after receiving treatment, an incident which we do not relate in any way to radio-iodine administration. The average interval between treatment and the establishment of euthyroidism for single-dose cures was about 4.5 months, but since patients are not seen more frequently than once a month after therapy the actual time is somewhat less than this.

Four cases relapsed after apparently successful first treatments—two after eight months and one each after nine and ten months respectively. Two had nodular glands, in one the gland was not enlarged, and one was a recurrence after partial thyroidectomy. All have become euthyroid after a second treatment and have remained so.

Hypothyroidism.—Seventeen cases (12%) became hypothyroid following therapy (Table I)—15 after one drink and one each after two and three treatments. The average interval between therapy and established hypothyroidism for single treatments was eight months, with a range of three

TABLE I.—*Clinical Results of Radio-iodine Therapy. Minimum Follow-up, One Year*

Type of G and	No. of Cases	% of Total	Clinical Result								
			Euthyroid			Hypothyroid			Still Toxic		
			Total	One Treatment	2 or More Treatments	Total	One Treatment	2 or More Treatments	Total	One Treatment	2 or More Treatments
Diffuse	66	47	57	43	14	7	6	1	2	—	2
Nodular	28	20	25	16	9	1	1	—	1	1*	—
Not enlarged	20	14	15	12	3	4	4	—	1	—	1
Post-operative recurrence	17	12	13	9	4	4	3	1	—	—	—
Single adenoma	6	4	6	5	1	—	—	—	—	—	—
Not known	3	2	2	2	—	1	1	—	—	—	—
Total	140	99	118 (84%)	87 (62%)	31 (22%)	17 (12%)	15	2	4	1	3

One patient with a nodular goitre died of a cerebro-vascular accident two days after treatment and has been omitted from the results column of the table.
* Refused further therapy.

months to three years. We have not used the term "myxoedema" to describe these cases, because few of these patients showed the full syndrome. All degrees of hypothyroidism can occur, and the amount of thyroxine necessary to keep such patients in normal thyroid balance varies. Thus, of our 17 hypothyroid cases the daily dose of L-thyroxine sodium required to maintain normal thyroid balance is only 0.1 mg. in 9 patients, and only one requires 0.3 mg.

Inadequate Treatment.—At the time chosen for assessment four patients were still toxic (Table I), though all were improved. One declined further treatment because she felt so well, and the other three were subsequently re-treated and became euthyroid.

Factors Influencing Failure Rate

Information about many of the factors which could influence the final result has been obtained in the course of the study, and has been subjected to a variance analysis by one of us (J. C. J.). The analysis was restricted to the results of the first or a single drink of the isotope, and the rad dose quoted is that estimated retrospectively after the therapy drink.

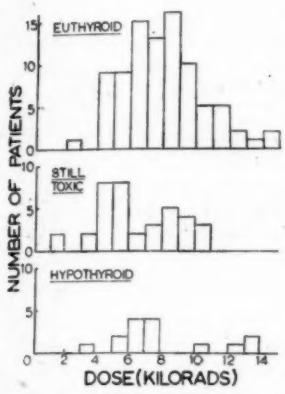

Figure showing relationship of rad dosage delivered to the thyroid gland to the clinical result, after the first drink of radioactive iodine to 140 patients.

The failure rate (ratio of patients who remained toxic to the total number treated) can be correlated with the administered dose in rads, the mass of the gland, and the concentration of protein-bound radio-iodine in plasma 48 hours after the tracer dose (P.B. ^{131}I). Table II and the Figure demonstrate a definite relationship between dose and failure rate, although, using the chi-squared test, no significant difference in the results was obtained in the groups that received between 6,000 and 11,000 rads.

Tables III and IV demonstrate the relationship of failure rate to gland mass and to P.B.^{131}I. There was shown to be no correlation between rad dosage and either gland mass or P.B.^{131}I, so in both instances results over the whole dose range are compared. Higher failure rates occurred with the larger glands and with higher blood concentrations, the results in both instances being significant on the chi-squared test at the 2% level.

No correlation was found between failure rate and age of patient, type of gland, or total half-life of ^{131}I in the gland, this last finding being different from that of Schmidt and Nadelhaft (1953), who showed a higher failure rate in patients in whom the half-life was long.

TABLE II.—*Relationship of Clinical Result to Rad Dosage*

Dose (Kilorads)	Still Toxic	Euthyroid	Hypothyroid	Failure Rate: Still Toxic/Total
1– 1·9 ..	2	0	0	1·0
2– 2·9 ..	0	1	0	0·0
3– 3·9 ..	2	0	1	0·67
4– 4·9 ..	8	9	0	0·47
5– 5·9 ..	8	9	2	0·42
6– 6·9 ..	2	15	4	0·10
7– 7·9 ..	3	13	4	0·15
8– 8·9 ..	5	16	0	0·24
9– 9·9 ..	4	10	0	0·29
10–10·9 ..	3	5	1	0·33
11–11·9 ..	0	5	0	0
12–12·9 ..	0	2	1	0
13–13·9 ..	0	1	2	0
14–14·9 ..	0	2	0	0
Total ..	37	87	15	0·27

TABLE III.—*Relation of Clinical Result to Mass of Gland*

Mass of Gland (g.)	Still Toxic	Euthyroid	Hypothyroid
30– 49	3	26	3
50– 69	7	30	9
70– 89	10	16	2
90–109	6	9	1
>110	11	6	0

TABLE IV.—*Relationship of Clinical Result to 48-Hour P.B.^{131}I*

Plasma P.B.^{131}I, % Dose Litre at 48 Hours	Failure	Euthyroid	Hypothyroid
<0·5	2	10	2
0·5–0·99	4	26	5
1·0–1·49	8	24	6
1·5–1·99	6	8	0
2·0–2·49	4	3	1
2·5–2·99	4	4	0
>3·0	6	3	0
Not known ..	3	9	1
Total ..	37	87	15

From the practical point of view the fact emerges that the size of the gland and the 48-hour P.B.^{131}I are important factors to be taken into account in prescribing the rad dosage. It is generally accepted that the failure rate is higher in nodular goitres than in diffuse goitres, or, in other words, nodular goitres should be given a higher radiation dose than would be judged necessary from a consideration of the size of the gland alone. Our results are consistent with this view. The relatively small number of cases studied and the wide range of rad dosage given make statistical evaluation inconclusive.

Other Effects of Therapy

Gland Shrinkage

Enlarged glands always become smaller and feel firmer after radioactive iodine therapy. The diffusely enlarged type usually returns to normal and nodular enlargement becomes less obvious. We have not observed early swelling of the gland after the drink, and we do not think there is any danger in using radio-iodine treatment in patients with compression of the trachea or with retrosternal glands.

Exophthalmos

Of the present series, 46 cases (33%) had exophthalmos of varying degree of severity, and in some it was the reason for their reference for radio-iodine therapy. It has improved considerably in many, and in no case in this series has it become worse.

In two subsequent cases, however, exophthalmos has progressed after otherwise successful treatment with the isotope. The first of these was a man who had light perception only in his right eye as a result of an accident at work six years previously. He presented with marked bilateral exophthalmic ophthalmoplegia and a severe degree of thyrotoxicosis with uncontrolled auricular fibrillation. Two months after a second therapeutic drink he developed a right hyphaemia with additional gross exophthalmos and chemosis. In view of the haemorrhage into the anterior chamber, blood studies were made; these showed normal bleeding, clotting, and prothrombin times, and red cell, white cell, and platelet counts were normal. A right enucleation was carried out. He is now in normal thyroid balance, and the degree of exophthalmos in his left eye has not altered since before therapy.

The second patient was a man with marked bilateral exophthalmos and thyrotoxicosis. Two months after otherwise successful radioactive iodine therapy the degree of exophthalmos increased, with the development of chemosis. The condition continued to progress in spite of every therapeutic measure, and decompression has been only partially successful. He still has gross exophthalmos, with considerable impairment of vision.

Pregnancy

As we have already pointed out, pregnancy is an absolute contraindication to the use of radioactive iodine. Two of our younger patients, however, unwittingly received treatment while pregnant. In one, conception had occurred some three weeks before the therapeutic dose, and in the other it followed about a week after a second (successful) treatment. In both cases pregnancy continued without upset and resulted in the full-term birth of healthy babies who have since developed normally.

Complications

In the previous presentation of our results with radioactive iodine (Blomfield *et al.*, 1951) one patient was reported who had a transient exacerbation of thyrotoxic symptoms following the therapeutic drink. No further episodes of this nature occurred in the present series, and indeed the method has been wholly free from any untoward immediate complication. A few patients complained of transient aching over the front of the neck for a few days after the therapeutic drink, but it was not severe enough to require the use of the mildest analgesics, and local tenderness could not be demonstrated in these or other cases.

Two patients developed urticaria a week after treatment, and in both it required continuous antihistamine therapy for many weeks before abating.

One patient developed transient thrombocytopenic purpura about 2½ months after treatment and about two weeks after becoming euthyroid. She had had a small dose of the isotope giving 5,700 rads to the thyroid gland, and her blood dose was only 5 rads. The condition cleared without therapy and she has remained in normal thyroid balance ever since (2½ years), with no further purpuric episodes. In view of the trivial blood dose and the fact that thrombocytopenic purpura is a well-known, if rare, complication of thyrotoxicosis (Caldwell and Meikle, 1953; Roberts, 1948; Evans and Perry, 1943), the grounds for indicting the isotope in this case seem to be slender. Blood counts have been carried out very frequently before and after isotope therapy for thyrotoxicosis, and in none has any significant alteration in the count taken place.

"Rheumatic" Complications.—Fifteen patients have complained of "rheumatic" symptoms—either articular or non-articular—after isotope therapy. The "rheumatic" lesions present in such cases are shown in Table V. Two

TABLE V.—*"Rheumatic" Lesions Following ^{131}I Therapy*

Rheumatoid arthritis type	2
Osteoarthritis type	4
Non-articular rheumatism	7
Gout	1
Prolapsed intervertebral disk	1
	15 (11%)

patients developed a rheumatoid-like arthritis. In one of these it was an exacerbation of an old lesion and occurred four months after the drink of isotope. The pain responded well to aspirin, and the patient was eventually left with no residual disability. The other case had no previous history of arthritis, and developed fairly typical rheumatoid changes some two months after therapy. The condition ran a prolonged course, but is now (2½ years after radioactive iodine treatment) steadily improving, with increasing functional capacity. Four patients have had symptoms of osteoarthritic lesions with involvement of single large joints (hip and shoulder), and one of these with shoulder arthritis developed, in addition, some progression of a Dupuytren's contracture that had been present for years in the fingers of her left hand. The commonest complaint after therapy is of non-articular "rheumatism." This most frequently involves the neck and shoulder region. In no case has it been of more than average severity, and in all it has occurred about four to six weeks after therapy. Each case has recovered completely.

Discussion

The problem of the choice of suitable cases for radio-iodine therapy becomes more important as it becomes increasingly used. There is still, however, considerable difference of opinion about the best method of treatment of thyrotoxicosis. The disadvantages of the antithyroid drugs are the high rate of relapse after they are discontinued and the incidence of granulocytopenia or agranulocytosis, deficiencies from which not even the latest additions to the series are wholly free.

Surgery has been made extremely safe by the preoperative use of antithyroid drugs, and in the best hands the mortality rate is less than 0.5%, although there is no doubt that where experience and specialized skill are not available it is considerably higher. The morbidity rate, however, remains significant, and tetany from parathyroid damage, section of the recurrent laryngeal nerve, wound sepsis, secondary haemorrhage, and adherent scars necessitating resection, as well as the pulmonary and other complications common to any surgical procedure, have all been recorded. It will be remembered, too, that bad operative risks are not usually subjected to surgery.

The obvious advantages of radio-iodine treatment are its immediate safety, and the certainty of being able to produce a remission with a minimum of discomfort to the patient, although this is achieved somewhat more slowly than by other therapeutic measures. Its disadvantages are the possible late development of carcinomatous changes in the gland and the somewhat high incidence of hypothyroidism. We shall therefore discuss these and the possible relationship of "rheumatism" to radio-iodine therapy in more detail before considering the best method of administering the isotope.

Carcinoma Hazard of Radioactive Iodine Therapy

Ionizing radiation is well known to have carcinogenic properties, and the use of radioactive iodine in the treatment of thyrotoxicosis raises the question of the degree of risk of subsequent neoplastic change in the thyroid to which the patient is exposed. The only suggestive evidence is from observations on animals. Thus, Goldberg and Chaikoff (1952) gave radio-iodine to rats and found that 7 out of 25 animals developed neoplastic changes in the gland. The doses of radiation, however, used by these investigators were enormous in comparison with those given for therapeutic purposes in man. The animals received 400 μc. of radio-iodine, which is comparable to a drink of 130 mc. to a human adult, and therefore about 14 times greater than the average single therapeutic dose. Doniach (1953), again using rats and giving doses of radio-iodine comparable to those used in the treatment of thyrotoxicosis in man, found no evidence of neoplastic change when radio-iodine was used alone, although he did note some increased simple adenoma formation. In his series, malignant change followed therapeutically comparable doses only when methyl thiouracil was given for long periods after the radio-iodine. This is in keeping with previous observations of carcinogenesis (Bielschowsky, 1944) that, while any one of two stimuli may alone be unable to produce thyroid carcinoma, their combined effect may do so. It is important to note that no experimental work in animals has demonstrated the development of carcinoma from the use of the isotope alone in doses comparable to those used therapeutically in man.

From our knowledge of carcinogenesis it probably takes about 20 years in man for a neoplasm to develop after exposure to ionizing radiations. Radioactive iodine has been employed in the therapy of thyrotoxicosis for 15 years, and so far no case of thyroid cancer has been reported following its use, though many thousands of cases have been treated by this method. One might have expected some cases already to have shown neoplastic changes if the risk of their development was significant, since skin cancer has been reported to have followed direct radiation after an interval of six years (Porter *et al.*, 1907).

It is known, further, that the type of radiation most likely to provoke carcinomatous change is small doses fractionated over a long period of time—so-called chronic radiation. The radiation from radioactive iodine is, however, of a more acute type, and is delivered in intense form over a short-lived period. It is thus, *a priori*, of the type least likely to result in neoplastic sequelae. The thyroid gland, moreover, appears to be relatively resistant to carcinoma, only about 0.4% (Tod, 1950) of all human cancer being of thyroid origin, and the Registrar-General's Statistical Review for 1952 shows that in that year 0.07% of all deaths, and 0.4% of total deaths from all neoplasms, were due to thyroid carcinoma. Furthermore, Quimby and Werner (1949) have shown that the risk of the development of thyroid cancer following conventional *x*-ray therapy for thyrotoxicosis, if it exists at all, is extremely low.

Finally, several careful studies of post-mortem thyroid histology have been carried out in cases which had received radio-iodine up to eight years before death, and no evidence of malignant change has been found, although some of these patients had received enormous doses of radiation with the object of producing myxoedema as a therapeutic measure for irreversible heart disease (Freedberg *et al.*, 1952; Dobyns *et al.*, 1953; Chapman *et al.*, 1954).

We feel, therefore, that the risk of neoplastic change in the thyroid following radio-iodine therapy is small, and we are impressed by the absence of any evidence that it is likely to occur in man following the use of radio-iodine alone in therapeutic doses. None the less, the final answer to the problem must await the passage of another decade and, in common with most workers in this field, we continue to limit the therapeutic use of radio-iodine to patients with a life expectation not exceeding 20 years with the exceptions stated in the introduction to this paper.

Post-Therapy Hypothyroidism

The rate of 12% post-therapy hypothyroidism in the present series is weighted by three patients out of our first seven cases who, from inexperience, were overtreated; in two of them repeat doses were given within an interval that we now know to be too short. If these first seven cases were excluded the overall incidence of post-therapy hypothyroidism would be reduced to 11% of 133 cases, a figure comparable to the one of 9% obtained in an analysis of the results of 1,720 cases taken from centres in U.S.A. and Europe, and reported by Seed and Jaffé (1953).

This incidence is higher than that following thyroidectomy, for which a mean rate of 5.4% of 6,442 cases emerges from a series of results from different centres cited by Bartels (1953). Post-operative myxoedema varied widely, however, in the different groups—from 2.9% (Grace and Weeks, 1941) to 21% (Crile and McCullagh, 1951). Crile (1949) has observed that the incidence of post-operative hypothyroidism is inversely proportional to recurrent thyrotoxicosis, and Bartels (1953) found it to be twice as high after second thyroidectomies.

It will be seen from Table VI that the average dose of radio-iodine which produced subsequent hypothyroidism was not greater than the average required to produce normal thyroid function in other cases, and, indeed, several patients have become hypothyroid after doses which have been inadequate to make others euthyroid. The explanation of this phenomenon may lie in individual variations in the biological sensitivity of different glands to radiation, though our inability to measure radiation doses accurately must be borne in mind in assessing the significance of comparative figures.

TABLE VI.—*Relationship of Clinical Result After a Single Treatment to the Size of the Millicurie Drink and to the Rad Dosage*

Clinical Result	Dose (Rads)		Drink (mc.)		Gland Size (g.)	
	Mean	Range	Mean	Range	Mean	Range
Euthyroid ..	8,000	2,800–14,300	9·6	2·4–22·4	62	30–175
Hypothyroid ..	7,950	3,800–13,700	9·2	5·2–15·9	55	30– 90
Still toxic ..	5,700	3,500–10,500	12·2	4·0–31·6	90	35–270

New light on this problem has been shed by the work of Greene (1953), who has studied the same problem following thyroidectomy. He has demonstrated a remarkably close correlation between post-operative myxoedema and the presence of lymphadenoid changes in the thyroid. Further, he has shown that, histologically, all grades of lymphadenoid change can exist, from single or scattered nodules to fully developed Hashimoto's disease, and that the incidence of post-operative hypothyroidism increases directly with the degree of lymphadenoid involvement, so that it is 100% in cases with fully developed Hashimoto's disease. Similar observations have been made by Bartels (1953). It is also a well-known surgical observation that the incidence of post-thyroidectomy hypothyroidism is not always referable to the amount of gland left behind, and, as Crile (1949) contends, it is the functional capacity of the remnant, and not its amount, that determines the state of post-operative thyroid balance. Clearly, the existence in the gland of progressive lymphadenoid changes will lead eventually to myxoedema in some cases, whether treated or not, and this end-stage will certainly be accelerated if a major part of the gland is excised surgically or destroyed by radiation. Greene (1953) stresses the fact that there is no clinical method of determining the existence of such changes in the gland before treatment, although he believes that they are more common in the older age group of thyrotoxic patients. We feel that these observations are especially applicable to our series because of the selection of the older age groups inherent in the use of the method. It would seem probable from Greene's work that a certain basic incidence of post-therapy hypothyroidism is inevitable with the treatment of thyrotoxicosis by any radical means, and that this incidence will increase with the age group of the patients treated.

Fraser *et al.* (1954), however, claim that preliminary treatment of patients with a drug of the thiouracil series combined with thyroxine makes the distribution and retention of radio-iodine in the thyroid gland more uniform. Only one of their 32 patients developed permanent myxoedema.

"Rheumatic" Sequelae

Of the "rheumatic" complications the non-articular variety almost invariably recovers promptly, and it is our impression that it occurs in association with a phase of transient post-therapy hypothyroidism. This does not apply to those cases which develop a rheumatoid-like picture. It seems most improbable that there is any direct relationship between the isotope *per se* and arthritic change. Numerous observers have reported a relationship betwen joint symptoms and thyroid function. The generally accepted opinion is that, while disturbed thyroid function has no aetiological significance in rheumatoid arthritis, pre-existing arthritis in thyrotoxicosis may be made either better or worse by treatment of the thyroid condition. The relevant literature is well summarized by Laine *et al.* (1954), who report in their own series of cases of thyrotoxicosis the aggravation or emergence of rheumatoid arthritis by thyroidectomy. Of our cases two patients developed rheumatoid arthritis after radio-iodine therapy, but in three others (one of the present series and two subsequently) who had rheumatoid arthritis of long standing no aggravation of joint symptoms occurred when they were euthyroid. Prévôt and Horst (1952) have also reported "fibrositic" lesions (10%) and rheumatoid arthritis (3%) after radio-iodine therapy; their cases of arthritis were victims of the disorder before isotope treatment. It seems probable that these "rheumatic" symptoms are in some way connected with alterations in thyroid function and may occur however this is induced.

Problems of Dosage

In our series of cases we have attempted to deliver to the gland a dose of between 6,000 and 8,000 rads in a single dose. We regard our single-treatment euthyroid

rate of 62% and our overall myxoedema rate (12%) as reasonably satisfactory. The chief difficulties which militate against precise dosage are the accurate assessment of gland size and the discrepancy between predicted and actual doses.

In spite of the use of scintillation counting techniques the errors in estimation of gland size must still be considerable, although we have not been able to check this in detail. The physical measurements, however, indicate the volume of the thyroid tissue actually taking up radio-iodine, and they are also of considerable value where the gland is in part retrosternal. Even so, it may be that this difficulty in accurately assessing gland size is one of the factors leading to overdosage and hypothyroidism. This point has recently been emphasized by Kelly (1954) in an analysis of the degree of error involved in "gland-size-estimating techniques," in which he found an average error of +49% in the method in use at the Veterans Hospital, Houston, Texas.

There is, in addition, a discrepancy between the predicted dose and that found retrospectively to have been delivered by the therapeutic drink (Blomfield *et al.*, 1953). In this series the mean ratio of the actual to the predicted dose was 0.98 ± 0.33 (S.D.). Part of this difference is due to the inaccuracy of physical measurement, but there remains a considerable biological factor. This mostly arises from changes in half-life between tracer and therapy drinks, although occasionally we find that the uptake of the therapy drink falls considerably short of that found following the tracer drink.

Current Procedure for Dosage Estimation

In order to determine the number of millicuries in the drink required to give the prescribed rad dose for cases treated after those recorded in this report, we have abandoned the use of detailed measurements of peak uptake and half-life at tracer level. For dosage prediction we now use the percentage of administered ^{131}I retained in the gland at 48 hours following the tracer drink. From the examination of the tracer and therapy measurements in our first 190 treatments we have derived a mean factor which relates the 48-hour percentage uptake to the total dose which the gland will receive for each millicurie of ^{131}I per g. of thyroid.* We now use this factor. With the method of prediction used in our first 190 treatments, the mean value of the ratio of actual to predicted dose was 0.98 ± 0.33 (S.D.). A retrospective application of our present formula for dose prediction showed that if this method had been used for these cases the mean value of the ratio would have been 0.96 ± 0.31 (S.D.). There is no statistical difference between these values. The method considerably reduces the amount of labour necessary, since the effective half-life need not be determined with the tracer dose.

For the retrospective assessment of the therapy dose actually given, we continue to measure peak uptake, and half life after the drink of the isotope.

Dosage Prescription

Our results indicate that for a given rad dose the failure rate is significantly higher for larger gland sizes and for high-protein-bound ^{131}I plasma concentration at 48 hours. We now aim to give 7,000 rads for diffusely enlarged glands, with 5,000 to 7,000 rads for smaller glands, particularly small post-operative recurrences. For large and multinodular glands we give 8,000 rads or more, and we may prescribe a higher dose for those with high protein-bound ^{131}I in their plasma after the tracer dose. We also tend to give rather more to elderly or severely toxic patients, or to those with severe cardiac involvement. The usual doses are smaller than those recommended by Fraser *et al.* (1954). This might be because the antithyroid drugs which these observers use before the radio-iodine is given may render the thyroid more resistant to the effects of ionizing radiation. Dale (1947) has shown that thiouracil increases radio resistance of enzymes in solution.

*This gives the formula:

$$\text{Expected dose in rads/mc.} = \frac{805 \times \text{48-hour \% gland uptake}}{\text{gland mass (grammes)}}$$

Conclusions

Radio-iodine treatment of thyrotoxicosis has now fully emerged from the experimental stage, and the general trend of recent work suggests that a wider range of patients might legitimately be treated by this method. We do not believe that there is any adequate evidence of a significant risk of the late development of carcinomatous changes in the gland. No one can yet be certain about the statistical risks involved, and it is clearly this point which is important. Provided it is no greater than, say, 0.1%, isotope therapy will still be safer than any alternative form of treatment. In time this figure will be known with a greater degree of certainty, and our recommendations about the selection of suitable cases must therefore remain as stated in the introduction to this paper. On balance, however, we favour the view of those who hold that radio-iodine therapy will ultimately be shown to be free from risk and that it will probably become the standard treatment for thyrotoxicosis.

The chance of the development of myxoedema from radio-iodine therapy is on the average somewhat greater than from operation, but we believe that with improved techniques it will become less, although it is possible that any method which destroys a part of the thyroid gland must inevitably lead to the development of myxoedema in a proportion of cases. Rheumatic complications are transitory and not related specifically to radio-iodine treatment.

Although we used an elaborate method of dose prediction in this series our results have not been better than those reported by others whose dose prescription has been based on gland size alone or other empirical formulae. As a result we have already simplified our technique so that the gland size and 48-hour uptake are the only two factors required for dose prescription. While it is probably sufficient in many cases to prescribe a therapeutic drink based solely on gland type and size, it is felt that experience with ^{131}I therapy is as yet too short to allow a general adoption of empirical dose prescription, and that those centres with the necessary experience and equipment should continue their efforts to achieve more accurate dose prediction.

Summary

The results of radioactive iodine treatment of 140 cases of thyrotoxicosis followed for a minimum period of one year are recorded.

A technique aimed at delivering a single dose of 6,000 to 8,000 rads to the gland has been used.

62% of patients were made euthyroid with one therapeutic drink, and ultimately 84% were euthyroid, 12% showed evidence of hypothyroidism, and at the time of review 4% were still toxic.

Statistical evaluation of the results shows that for a given rad dosage the success of a first treatment was related to the mass of the gland and to the percentage of protein-bound radio-iodine in the blood 48 hours after the administration of a tracer dose.

It is concluded that at present there is no convincing evidence that radio-iodine treatment is likely to lead to the development of late malignant changes in the thyroid gland.

Some cases developed both articular and non-articular rheumatism, probably unrelated to isotope therapy.

The present criteria for the selection of cases and dosage assessment are discussed.

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ANTIBODY RESPONSES AND CLINICAL REACTIONS WITH SALINE AND OIL ADJUVANT INFLUENZA VIRUS VACCINES

SECOND PROGRESS REPORT BY THE MEDICAL RESEARCH COUNCIL'S COMMITTEE* ON CLINICAL TRIALS OF INFLUENZA VACCINE

In the past few years a number of reports have appeared on the adjuvant effects obtained by adding various chemical substances to bacterial or virus vaccines. These materials produced an enhanced antibody response to the antigens used, but severe local reactions were at times encountered in man. A relatively stable water-in-oil emulsion prepared by using an emulsifier known as "arlacel" and a mineral oil ("bayol F") was introduced by Freund *et al.* (1948a, 1948b), and this was found by Salk and Laurent (1952) to be relatively free from undesirable side-effects. Salk *et al.* (1952) used an influenza virus vaccine to which arlacel and bayol F had been added, and confirmed the adjuvant effect which these materials produced in man. They found that the antibody response was enhanced in amount so that the titre of serum antibodies after use of one-tenth the normal amount of antigen in an adjuvant menstruum was greater than that produced by the full amount of antigen in a saline medium. The antibody response was also prolonged in duration, and twelve months after inoculation the level had fallen only slightly from the peak titre. Salk further stated (1953) that the breadth of antibody response was increased so that an injection of a single antigenic type of influenza virus A caused antibodies to be formed against a related yet distinct antigenic type of virus A as well as against the homologous antigen.

These reports led the Medical Research Council's Committee on Clinical Trials of Influenza Vaccine to explore the use of oil adjuvant influenza vaccines in this country. It was decided first to compare the serological response to a single (monovalent) influenza A vaccine in saline to which aluminium phosphate had been added with that found when the vaccine was suspended as a water-in-oil emulsion. A supply of purified arlacel and of a mineral oil was obtained through the courtesy of Dr. Salk. The Liverpool strain of influenza virus A (A/Eng/1/51) was selected as suitable for use partly because this strain had been used with apparent success in earlier trials in Great Britain and partly because egg- and mouse-adapted lines or substrains were available.

Since the previous report of this Committee (1953) evidence has been obtained in the laboratory that mouse-adaptation of an influenza virus appears to confer an improved antigenicity upon the strain when the latter is compared with the same virus passaged only in eggs. This was first shown to be true by immunization experiments in mice (Isaacs and Sampaio, 1953), and later the serological response in man to a mouse-adapted virus (Liverpool, A/Eng/1/51) was compared with that exhibited to the egg-adapted line of the same strain. Table I shows the geometrical mean titre of serum antibodies in 57 men before and after inoculation subcutaneously with an egg-virus vaccine suspended in saline and similar titres in a further 78 men receiving a mouse-adapted virus vaccine containing the same concentration of virus. The antibody response to the latter virus appeared to be superior to that produced by the egg virus, as determined by the haemagglutination-inhibition test.

TABLE I.—*Geometric Mean Haemagglutination-inhibition Titres of Individuals Vaccinated with Saline Vaccines from Egg- and Mouse-adapted Lines of A/Eng/1/51 Virus and Tested with Homologous and Heterologous Viruses*

Virus	Serum	Vaccine: A/Eng/1/51 Mouse-adapted		Vaccine: A/Eng/1/51 Egg Line	
		Antibody Titre	Ratio	Antibody Titre	Ratio
Homologous	Pre-inoculation	9·5		17·8	
	Post-inoculation	107	11·2	89·0	5·0
Heterologous	Pre-inoculation	17·8		10·0	
	Post-inoculation	100	5·6	47·9	4·8

Notes:—(i) Sera with titres < 10 were given an arbitrary score of 5.
(ii) The antigenic relationship between the egg line and the mouse-adapted A/Eng/1/51 virus was tested by haemagglutination-inhibition tests with ferret antisera. The titres were as follows:

Virus	Ferret Antisera: A/Eng/1/51 Egg Line	A/Eng/1/51 Mouse-adapted
A/Eng/1/51 egg line	5,120	3,840
A/Eng/1/51 mouse-adapted	7,680	10,240

These previously unpublished experiments reported to the Committee in 1953 suggested that a further trial comparing mouse- and egg-virus vaccines made from the same strain but to which oil adjuvants had been added would give useful additional information. It was therefore decided to use the mouse-adapted line of the Liverpool strain of virus A both in a saline and in an oily medium, and to use the egg strain in an oily medium only. This study was designed to test the antibody response to these three vaccines and to obtain information upon the local and general reactions consequent upon their inoculation.

*Members of the Committee: Professor C. H. Stuart-Harris (chairman), Dr. C. H. Andrewes, Dr. B. E. Andrews, Brigadier G. T. L. Archer, Dr. W. H. Bradley, Brigadier A. E. Campbell, Surgeon Captain T. L. Cleave, Professor R. Cruickshank, Professor A. Bradford Hill, Dr. F. Himmelweit, Dr. A. Isaacs, Dr. F. O. MacCallum, Dr. J. C. McDonald, Dr. W. J. Martin, Dr. J. J. O'Dwyer, Professor Wilson Smith, Dr. I. N. Sutherland, Group Captain J. S. Wilson, Brigadier A. E. Richmond (Secretary).

General Organization of the Trials

Inoculations were carried out in November, 1953, on 399 volunteer students at nine London medical and other university schools and in two other universities (Sheffield and Manchester); each of these eleven centres contributed from 24 to 55 persons. Approximately equal numbers of volunteers in each centre were given single inoculations of one of the three vaccines, which were distributed on a random basis by using specially prepared lists. Blood samples were to be collected from each volunteer before inoculation and two weeks, four weeks, three months, six months, and one year after inoculation. It was to be expected that occasional bleedings would be missed, and in fact this occurred to the extent of 5.5% of all bleedings which should have been taken.

Similarly, although it was advised that examinations for local reactions should be carried out on seven occasions in each volunteer during the year of observation, these were at times missed, but if such an examination in an individual did not take place on one occasion it took place when next due. It is clear that the above factors had little or no influence on the results of the investigations, and they were accordingly disregarded. Sera were tested in four laboratories: the World Influenza Centre, Mill Hill; the Virus Reference Laboratory, Colindale; the Wright–Fleming Institute of Microbiology, St. Mary's Hospital, London; and the University Department of Medicine at Sheffield. The individual records of the volunteers were made on standard cards, which were kept at each centre by the medical officers who gave the inoculations and who were responsible for the observation of the reactions.

The Vaccines

The vaccines were prepared by Dr. F. Himmelweit at the Wright–Fleming Institute of Microbiology from fertile eggs inoculated allantoically with the appropriate virus. They were dispensed in disposable cartridges in the individual volumes of 0.25 ml. or 1 ml. required for the injection. The three vaccines were as follows:

Vaccine A.—A water-in-oil emulsion containing 2,000 haemagglutinating units of mouse-adapted influenza virus (A/Eng/1/51) per dose (0.25 ml.).

Vaccine B.—As above, but prepared from the egg-adapted lines of the same virus strain. (Dose 0.25 ml.)

Vaccine C.—Each dose (1 ml.) contained 20,000 haemagglutinating units of the mouse-adapted virus (A/Eng/1/51) in 1 ml. of saline to which 10 mg. of aluminium phosphate had been added.

Vaccines A and B were inoculated intramuscularly into the triceps and vaccine C was given by deep subcutaneous injection into the upper arm.

The virus suspensions of the two lines were obtained by centrifugation according to the method of Stanley (1944). Virus was sedimented in a Sharples centrifuge from pools of formolized (1:10,000 formaldehyde) allantoic fluids, and was resuspended in M/10 phosphate buffer solution, *p*H 7.2. Haemagglutination units were assessed by the "pattern method" in use at the World Influenza Centre (W.H.O., 1953). A haemagglutinating unit was defined as that amount of haemagglutinin present in 0.25 ml. of the virus suspension (excluding the cell suspension) that gives an end-point midway between complete agglutination and absence of agglutination.

Salk's procedure was closely followed in preparing the emulsified vaccines A and B. Virus suspensions, oil, and emulsifying agent in a ratio of 10:9:1 were mixed by using a syringe to which a 17-gauge needle, ½ in. (1.3 cm.) in length, had been fitted.

The aluminium phosphate contained in vaccine C was prepared according to Holt's method (1950) by mixing equimolar solutions of $AlCl_3.6H_2O$ and $Na_3PO_4.12H_2O$. The resultant precipitate was washed in neutral M/10 phosphate buffer solution before being added to the virus suspension in saline.

Merthiolate was added to each of the vaccines to give a final concentration of 1:10,000 in the aqueous phase.

General Reactions

General reactions characterized by headache, either alone or accompanied by such symptoms as lassitude, malaise, sweating, giddiness, nausea, and so on, were experienced in relatively few instances. Table II shows the incidence after stated periods with each vaccine. Pyrexia was found in only one or two instances. Malaise, lassitude, and nausea alone or in combination were experienced in a few cases, and various other symptoms occurred in a small proportion of the volunteers. There was no significant difference between the vaccines so far as these general reactions were concerned.

TABLE II.—*Incidence of General Reactions*

Vaccine	No. of Volunteers	General Reaction 24 Hours after Inoculation		General Reaction 48 Hours after Inoculation	
		No.	%	No.	%
A (mouse-adapted oil) ..	136	10	7·4	8	6·6
B (egg-adapted oil) ..	132	14	10·6	6	4·5
C (mouse-adapted saline)	131	10	7·6	10	7·6

Local Reactions

Table III shows details of the local reactions which were characterized by erythema, swelling, or induration. Erythema and swelling, either alone or in combination, were chiefly found in volunteers receiving vaccine C—the saline-alum vaccine—and were observed during the first 24 to 48 hours after inoculation. Erythema was found in only one volunteer after this time; it was present at two weeks, but not subsequently, in a volunteer who received vaccine C.

TABLE III.—*Incidence of Local Reactions After Inoculation*

Vaccine	No. of Volunteers	Erythema		Swelling		Induration	
		No.	%	No.	%	No.	%
A (mouse-adapted oil) ..	136	7	5·1	8	5·9	13	9·6
B (egg-adapted oil) ..	132	6	4·5	13	9·8	19	14·4
C (mouse-adapted saline)	131	53	40·5	59	45·0	43	32·8

Differences

	Erythema	Swelling	Induration
A–B	0·6±2·6 (not sig.)	3·9±3·3 (not sig.)	4·8±4·0 (not sig.)
C–A	35·4±5·1 (sig.)	39·1±5·3 (sig.)	23·2±5 0 (sig.)
C–B	36·0±5·1 „	35·2±5·5 „	18·4±5·2 „

Swelling at the site of inoculation was frequently present for the first 48 hours, after inoculation with the saline-alum vaccine (C) and persisted in two volunteers for two weeks. It was encountered for the first 48 hours after inoculation in a much smaller percentage of those receiving the oily vaccines and disappeared within two weeks in all save two instances. These are described in detail below as chronic reactions.

Induration at the site of inoculation was found at some time or another in 43 (32.8%) of volunteers receiving vaccine C (saline-alum), in 13 (9.6%) of volunteers receiving vaccine A (mouse-adapted oil), and in 19 (14.4%) of those inoculated with vaccine B (egg-adapted oil). The induration was found at 24 hours in 25 persons receiving vaccine C, and in each of two groups of 9 persons receiving vaccines A and B respectively. The figures at 48 hours for vaccines C, A, and B were 21, 11, and 17 respectively. Two weeks after inoculation the figures were 25, 3, and 5 respectively, and had declined to 13, 2, and 2 at one month.

Chronic induration was still present at three months in 10, 2, and 2 volunteers receiving vaccines C, A, and B respectively, at six months in 8, 2, and 1, and at one year in 4, 2, and 0. At this time, one year from inoculation, the indurations were less than 1 cm. in diameter, and were more or less sharply defined. One (C) had disappeared and the

other had declined in size still further when the arms were inspected fifteen months from the time of inoculation.

Comparison between the indurations noted in the three groups of volunteers must take into account the fact that the saline vaccine C was given subcutaneously, whereas the oily vaccines were inoculated intramuscularly, so that reactions to the latter inocula were less accessible to palpation.

Two volunteers, one given vaccine A and one vaccine B, had reactions which appear worthy of detailed description. The first case was that of a volunteer given vaccine A in whom some swelling and induration were found immediately after inoculation; nothing was again noted until one year later, when the whole of one insertion of the triceps was discovered to be very slightly and painlessly thickened. Three months later a short band of thickened fibrous tissue in the triceps (approximately 50–60 mm. by 1–2 mm.) was still present. There was some doubt about whether this had any relation to the inoculation, but, in view of its site and in the absence of any other explanation of its presence, it was so recorded. The case is not included in those with induration at one year, though it was included in the early stage referred to.

The second case was that of a volunteer who had received vaccine B and exhibited a local reaction from the start. At three months it was in the form of a hard swelling, diffuse and ill-defined, which seemed to involve the greater part of one head of the triceps. It was estimated to be about 5 cm. in diameter. At six months it had decreased to 3 cm., and at one year and again three months later there was little to note except that the muscle generally was slightly firmer than normal.

These two reactions were the only instances of possible abscess in those receiving oily vaccines, and neither led to liquefaction or cyst formation such as were described by Philip *et al.* (1954) in persons receiving oil adjuvant influenza vaccines.

Serological Responses to the Vaccines

Haemagglutination-inhibition tests were carried out at the four participating laboratories, using standard antigens and standard pools of human sera for control purposes prepared at the Wright–Fleming Institute. The antigens were prepared from the same seed virus as that used for the vaccines and were dried from the frozen state and kept at 4° C. until use. The test technique was that employed at the World Influenza Centre, using plastic plates (W.H.O., 1953). Eight haemagglutinating units of homologous virus were used with each serum dilution, and the sera were inactivated by heating at 56° C. for 30 minutes, but were not otherwise treated. They were stored frozen at −25° C. until use. More than one serum specimen from a particular volunteer in addition to the control sera was always included in a test, and repeat tests on the same serum samples were also used to check the procedures. The results obtained in the four laboratories are presented both separately and in total in Table IV, which gives the geometric mean titres of the various serum samples. The results were considered to be reasonably concordant and permit the following conclusions:

(*a*) The peak in antibody titre was obtained at two weeks with vaccine C and at three months with vaccines A and B. At the peak the increase in antibodies was some nine times the initial mean titre with vaccine C. This represented a somewhat better response than that recorded in the serological trials carried out with a similar egg-grown and not mouse-adapted virus A vaccine in 1952 (M.R.C. Committee on Clinical Trials, 1953). Both the two oil-containing vaccines gave a greater increase in mean antibody titre than the saline vaccine, that for A being 25 times and for B nearly 12 times the initial titre.

(*b*) The mean antibody titre remained elevated above the initial titre for at least one year after inoculation with each vaccine. The mean titre in those given vaccine C was still about five times the initial level, while the corresponding figures for A and B were approximately eleven and seven times. The fall in antibodies in those receiving the oil adjuvant vaccines was, however, greater at one year than had been expected.

(*c*) The egg-adapted virus strain used in vaccine B was not so effective an antigen as the mouse-adapted strain used in vaccine A.

(*d*) In one centre (Sheffield) a number of sera obtained both before and at intervals after vaccination were titrated with a heterologous influenza virus A strain. The latter was the A/Eng/1/54 recovered from a small localized outbreak of influenza at a hospital in Essex in 1954. The results obtained with homologous virus and with the heterologous virus, which was a line passaged only in eggs, showed that the antibody responses in nine volunteers given the saline mouse vaccine (C) were insignificant as measured by the heterologous virus except in two instances. Similar insignificant responses were found in three volunteers given the oily (mouse) vaccine (A) whose sera were tested against the heterologous strain. Of nine volunteers inoculated with the oily (egg) vaccine (B) and exhibiting good homologous antibody responses five gave relatively good heterologous responses. These few observations indicate that oil adjuvant vaccines cannot be relied upon to increase the breadth of antibody response to heterologous virus A strains.

TABLE IV.—*Summary of Results of Virus A Vaccines Under Comparative Investigation for Antibody Production*

Centre	Vaccine	Original No. of Volunteers	Geometric Mean Titres					
			0	2 Weeks	1 Month	3 Months	6 Months	1 Year
Sheffield University	A	35	19·0	62·4	163·9	422·4	330 9	205·9
	B	31	46·6	126·0	251·3	539·6	512 8	346·1
	C	30	24·41	180·0	164·0	134·1	111·6	90·2
Wright–Fleming Institute	A	20	7·1	39·0	98·0	292·5	235·7	127·3
	B	21	5·2	19·6	40·4	116·2	100 6	61·0
	C	20	13·4	120·6	118·6	110·7	90·9	87·9
Virus Reference Laboratory, Colindale	A	38	5·7	27·7	62·7	135·0	131·8	75·4
	B	35	6·5	16·7	59·5	102·6	86·3	55·7
	C	38	8·7	120·0	123·8	87·2	74·0	59·3
World Influenza Centre, Mill Hill	A	43	21·8	76·0	155·0	496·6	270·7	165·2
	B	45	27·7	49·3	84·5	201·4	187·3	111·2
	C	43	20·4	151·4	151·0	150·0	106·5	68·9
All centres combined	A	136	12·3	49·6	114·7	308·1	232·3	140·8
	B	132	16·2	39·5	87·7	193·0	176·5	116·5
	C	131	15·1	142·2	140·0	119·2	95·9	73·9

Rise of antibodies (Geometric mean titre at specified times divided by geometric mean titre before inoculation)

		Period after Inoculation				
		2 Weeks	1 Month	3 Months	6 Months	1 Year
Sheffield University	A	3·2	8·6	23·2	17·4	10·8
	B	2·7	5·4	14·2	11·0	7·4
	C	8·4	7·6	6·2	5·2	4·2
Wright–Fleming Institute	A	5·5	13·8	41·5	33·7	18·2
	B	3·8	7·8	22·2	19·3	11·7
	C	9·0	8·9	8·3	6·8	5·9
Virus Reference Laboratory, Colindale	A	4·9	11·0	23·7	23·3	13·7
	B	2·6	9·2	15·8	12 9	8·8
	C	13·8	14·2	10·0	8·0	6·3
World Influenza Centre, Mill Hill	A	3·5	7·2	22·0	12·3	7·6
	B	1·8	3·1	7·2	6·4	4·0
	C	7·2	7·4	7·1	5·0	3·3
All centres combined	A	4·0	9·3	25·0	18·9	11·4
	B	2·4	5·4	11·9	10·9	7·2
	C	9·4	9·2	7·9	6·4	4·9

Discussion

The results of this study appear to afford a confirmation of certain of the observations made by Salk in the U.S.A. In particular, the adjuvant effect of the emulsified vaccines is clearly demonstrated, and the economy thereby effected in the amount of antigen needed to produce the requisite antibody response in man is obvious. Had the saline vaccine used for comparison with the oil vaccine contained as little virus antigen as did the latter, it is likely that only a much smaller antibody response would have resulted. The oily

vaccine was, moreover, matched against the best saline vaccine from the standpoint of antigenic content which could be made, and its superiority was thereby abundantly demonstrated.

Salk's observations concerning the breadth of antibody response could not, however, be substantiated so far as one other virus A strain was concerned. Use of adjuvants in influenza vaccines is probably not, therefore, a solution to the problem of the immunological specificity of the inactivated influenza virus vaccine.

The rate of reactions recorded in this trial was considered to be satisfactory and to be low enough to permit exploration of a field trial using oily vaccines. At the same time, the occasional chronic reaction, often discovered only on clinical examination and not causing any grave inconvenience, appears likely to be encountered, but even the alum-containing saline vaccine is not free from such chronic effects.

The antibody response to the emulsified vaccines appears relatively less persistent than had been anticipated. This may have been due to a deficiency of the adjuvant principle contained in the emulsions which were used. The arlacel provided by Dr. Salk was of exceptional purity, but the efficiency of emulsions may be related in part to the content of impurities in the emulsifier. It is therefore possible that an emulsion containing more of these impurities might give a more durable antibody response. The reaction rate with such preparations might, however, be greater than with purer and therefore more easily assimilated materials. More work is clearly desirable on this and other matters connected with adjuvant vaccines.

The comparison of the antibody titres obtained with egg- and mouse-adapted virus vaccines favours the latter. It is, however, difficult to be sure of the significance of the higher antibody levels with mouse-adapted virus. The differences with the two lines are not so striking as in experiments with mice. Since a number of factors such as small antigenic differences and differences in the avidity for antibody may be concerned, it seems wisest to delay interpreting these results and to compare instead the protective value of the two lines of virus. The results of trials of this nature are awaited at the moment.

Summary

A trial of approximately one year's duration was carried out to compare the antibody responses and clinical reactions to three virus A influenza vaccines, the strain A/Eng/1/51 being used as the antigen in each case. Two of the vaccines were of the emulsified type—from mouse-adapted and egg-adapted viruses respectively—and the third—from a mouse-adapted virus—was of the saline type with aluminium phosphate. A total of 399 volunteers in eleven volunteer centres were involved. The emulsified vaccines gave a greater and more sustained antibody response than the saline vaccine in spite of the fact that they contained only one-tenth of the amount of virus antigen. A decrease in the antibody levels found one year after inoculation occurred in all vaccinated groups. No indication of an increased breadth in antibody response to a heterologous virus strain in those given oily vaccines was demonstrated by a small series of tests. The local reactions were more numerous in those given the saline than in those given the oily vaccines, but with the latter vaccines unusually extensive and persistent local reactions occurred in two volunteers.

The Committee wishes to acknowledge the very generous support and co-operation it has received in this trial from many sources. In particular it is anxious to record its special thanks to all the students at the eleven centres who at much personal inconvenience took part in the trial; to the student health officers and their staffs at University College, London, and at Sheffield and Manchester Universities, whose help was invaluable; and, finally, to the medical staffs concerned at St. Bartholomew's, St. George's, Guy's, King's College, London, St. Mary's, Middlesex, and University College Hospitals, who never failed in affording all possible assistance in the organization and carrying out of the trial.

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DIAGNOSTIC METHODS IN AN INFLUENZA VACCINE TRIAL*

BY

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Large-scale field trials of a polyvalent influenza virus A vaccine were conducted by the Medical Research Council Committee on Clinical Trials of Influenza Vaccine during the winter of 1952–3 (Report, 1953). In these trials the attack rate of clinical influenza was 3% in 6,340 volunteers who received the virus vaccine and 4.9% in 6,370 who received a control bacterial vaccine. It therefore seemed clear that the vaccine had a protective effect. The method of diagnosis used in these trials was entirely clinical, unaided by laboratory tests. The Committee chose the method deliberately because of the practical difficulty in obtaining and testing blood samples and throat washings from sick volunteers in trial centres scattered throughout the United Kingdom, and because it was doubted whether serological methods were valid for comparing the influenza attack rates in two groups of persons, one of which had been vaccinated with influenza virus. The Committee agreed that a small-scale trial using the same vaccines should be carried out simultaneously within the main scheme to study the practicability of basing diagnoses on both clinical and laboratory methods, and to compare results of serological tests in the vaccinated and control groups. This report describes a trial carried out in Vauxhall Motor Works, Luton, with these aims in view.

Organization of the Trial

Early in October, 1952, the firm was asked whether facilities could be given for an influenza vaccine trial which would include the home visiting of the vaccinated volunteers when they were away from work, and the taking of specimens where indicated for laboratory examination. The management and chief medical officer agreed, but thought that the works council, representing the employees, should be consulted about the home inquiry. The proposed scheme was therefore brought before the works council. It was explained that the home visits would not be made by one of the firm's doctors and that the findings on any individual person would not be disclosed to the employers. The works council approved the scheme, and a circular

*A report to the Medical Research Council Committee on Clinical Trials of Influenza Vaccine.

letter was sent to all employees asking for volunteers. The scheme was discussed with the medical officer of health of Luton and with general practitioners at a meeting of the local branch of the British Medical Association. As soon as the names of volunteers were known, an explanatory letter was sent to all doctors with patients who had offered to take part.

Five hundred and five persons came forward, rather fewer than had been hoped for. All were interviewed, and 16 excluded because of a past history of tuberculosis or sensitivity to eggs, or at the request of their own doctor. Thirty-five volunteers failed to attend for inoculation, and six of those who attended were not injected because they did not appear to be fit. In all, 458 were inoculated, but as three left the firm during the follow-up period complete records are available for only 455, 226 of whom received the trial vaccine and 229 the control.

Vaccines and Inoculation Procedure

Precisely the same vaccines and inoculation procedure were used as in the main trial. The trial vaccine contained equal proportions of threefold concentrations of the F.M.1 strain and the egg-adapted Liverpool (1951) strain. Each dose of 1 ml. contained 9,600 haemagglutinating units of the F.M.1 strain and 12,000 units of the Liverpool (1951) strain adsorbed on to 10 mg. of aluminium phosphate. The control vaccine was a low-potency bacterial vaccine of the anticatarrhal type. Each dose of 1 ml. contained 12.5 million *H. influenzae*, 25 million pneumococci, and 2.5 million streptococci, in addition to 10 mg. of aluminium phosphate and merthiolate to a final concentration of 1 in 10,000.

The vaccines were given on December 8, 9, and 10 by a single deep subcutaneous injection into the left upper arm. The vaccine chosen for each volunteer was determined by use of inoculation registers, one for each sex, in which the random sequence in which the two vaccines were to be given had been set out.

Reactions

All those inoculated were seen 48 hours later by one of us and were asked about local and general reactions. These were assessed by their severity and recorded as nil, slight, and insufficient to interfere with normal activities, moderate and interfering with normal activity, or severe and causing absence from work. Most of the inoculated had a slight local reaction, but no local or general reaction was severe enough to cause absence from work. The incidence and severity of reactions still present 48 hours after inoculation are shown in Table I.

TABLE I.—*Percentage of Persons in Whom Reactions were Observed*

Severity	Local		General	
	Trial Vaccine	Control Vaccine	Trial Vaccine	Control Vaccine
Nil	33%	25%	89%	88%
Slight	66%	73%	10%	11%
Moderate ..	0%	2%	1%	1%
Severe	0%	0%	0%	0%

At an interview during the second week in March—that is, three months after inoculation—six persons mentioned that they still had a lump at the site of injection. In each case inspection showed a round indurated subcutaneous swelling about an inch (2.5 cm.) in diameter, and in one the swelling was acutely inflamed. As this information was volunteered and not obtained by inquiry it seems possible that others may have had similar reactions.

The Follow-up

Those inoculated were observed for 12 weeks, from December 15 to March 6. Each day the records department prepared a list of persons in the study who were absent from work, excluding those known to be absent for non-medical reasons. All those on the list were visited by one of us the same day and the cause of absence with details of any illness was recorded. Of 217 persons so visited 59 were not found at home, but a satisfactory explanation for 36 of these was given by another member of the household. A blood sample and throat washings were taken from any person who was thought possibly to have influenza, and from every fourth person with any other respiratory illness. A second specimen of blood was taken between 19 and 24 days later.

At the end of the trial the volunteers' attendance record cards were examined and a note was made of the date and duration of all absences of half a day or more. It was discovered that in about a quarter of the absences the volunteer's name had not appeared on a daily list and as a result they had not been visited during their illness.

Paired samples of serum were tested for complement-fixing antibody to the soluble antigens of influenza viruses A and B, and also for haemagglutination-inhibiting (H.I.) antibody to the two virus strains incorporated in the vaccine (Liverpool (1951) egg-adapted, and F.M.1), a 1953 (A/Eng/1/53) virus strain, and a strain of influenza virus C. A fourfold or greater rise in antibody was regarded as positive evidence of infection with influenza virus. Virus isolation from garglings was attempted by the amniotic inoculation of fertile hens' eggs.

The Epidemic

Cases of clinical influenza in volunteers were seen between the weeks ending January 3 and February 28, 1953. All but one of the illnesses in which serological evidence of influenza was obtained had their onset between weeks ending January 24 and February 28. The single exception was in a volunteer who was inoculated with the trial vaccine on December 9 and who developed symptoms of a common cold six days later, on December 15. Blood specimens were taken from him on December 16 and 30, and it seems probable that the rise in antibody observed was due to the vaccine rather than to natural infection. All cases diagnosed as influenza serologically were due to virus A, except one which was positive for virus C infection. After the usual fluctuations around Christmas and the New Year the number of claims for sickness benefit received by the Luton office of the Ministry of Pensions and National Insurance began to rise in the week ended January 27, reached a peak in mid-February, and then fell away. There is thus general agreement that the epidemic period extended from the middle of January to the end of February—that is, 7 to 12 weeks after inoculation—and this is illustrated in the accompanying Chart.

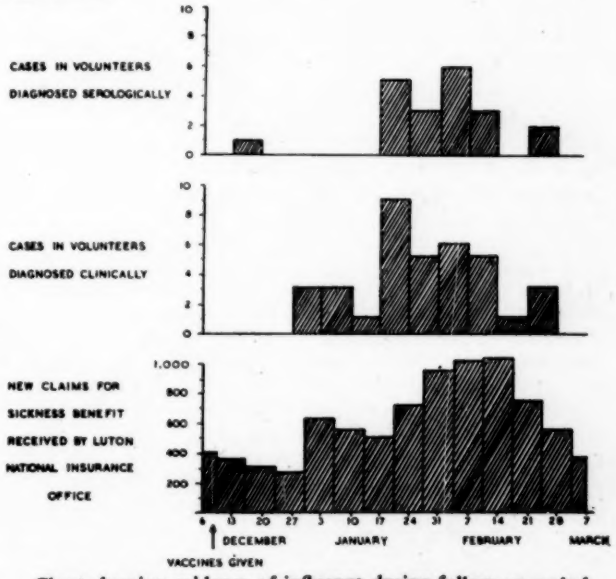

Chart showing evidence of influenza during follow-up period.

Results

Eighty-two cases of acute respiratory illness causing absence from work were found in the course of the home-visiting. A clinical diagnosis of influenza was made in 36 of these, and throat washings were obtained from all and paired sera from all but one. Paired sera and throat washings were also obtained from 21 persons in whom the diagnosis of influenza was considered possible but improbable and from 6 out of 25 thought to be suffering from a cold or sore throat. Thus paired sera were obtained from 62 persons and throat washings from 63. Seventeen pairs of sera were positive when tested for haemagglutination-inhibition with a current 1953 influenza virus A strain, and 12 pairs with each of the strains of virus used in the vaccine. Twelve positive results were also obtained by complement-fixation test, using virus A soluble antigen. In all, 20 pairs of sera gave a positive result in one or more tests for virus A infection; five were positive in all four tests, eight in three tests, two in two tests, and five in one test only. All serum pairs were negative in tests for influenza virus B infection (soluble antigen C.F.T.), but one pair from a clinically typical case of influenza was positive for influenza virus C infection (H.I. test). Influenza virus A was isolated from four cases diagnosed clinically and serologically as influenza. One of the four had received the trial vaccine, and it is of interest that the only serological test positive in this case was the H.I. test using the current strain.

Of the 36 clinical cases of influenza 15 had received the trial vaccine and 21 the control vaccine, absence rates being 6.6% of 226 and 9.2% of 229 respectively. Though the difference between these rates might have been due to chance (difference ÷ standard error = 2.6/2.5 = 1.0), it is compatible with that observed in the main trial, where, because of the much larger numbers involved, the corresponding rates, 3% and 4.9%, were found to be statistically significant. In the main trial these figures amounted to a 40% reduction in absences due to influenza in the trial group, and in the Luton trial to a 30% reduction.

Serological evidence of influenza virus A infection was obtained in 16 of the 35 clinical cases tested, but in Table II it may be seen that, whereas 16 out of 34 pairs (47%) taken from persons who received the control vaccine were positive, only 4 out of 28 (14%) who had received the trial vaccine were positive. Serological evidence of influenza was thus found in 4 out of 226 persons in the trial group, and in 16 out of 229 persons in the control group, rates of 1.8% and 7% respectively. The difference between these rates is appreciably greater than that observed between the absence rates due to clinical influenza, and is statistically significant at the 5% level (difference ÷ standard error = 5.2/1.4 = 3.7). However, as pointed out below, the validity of this estimate of the protective value of the vaccine depends on the interpretation of serological results in vaccinated persons.

TABLE II.—*Serological Results in Relation to Clinical Diagnosis*

Clinical Diagnosis	Vaccine	Absences	No. Tested	No. Positive*	% Positive
Probably influenza	Trial	15	15	3	20%
	Control	21	20	13	65%
Probably not influenza	Trial	26	13	1	8%
	Control	20	14	3	21%
Total respiratory illness	Trial	41	28	4	14%
	Control	41	34	16	47%

* Number of persons showing a fourfold or greater rise in antibody in at least one serological test.

Discussion

Experience showed that, on the scale employed in this field trial, the method was practicable. It could be improved by taking steps to ensure more complete notification of absences from work, and to learn of short illnesses which occur during week-ends and so do not cause absence on a working day. Its application on a scale large enough for evaluation of a vaccine adequately would be expensive in the number of field workers required and would entail a great deal of laboratory work. The cost might be justified if greater precision was thereby obtained than in the main studies in which reliance was placed on clinical diagnosis. As the figures presented are small the difference observed between the clinical and the serological assessment cannot be accepted without further evidence, but, if confirmed, there would appear to be two possible explanations for it. If the serological method was accurate and unbiased a clinical diagnosis of influenza must have been applied to many illnesses which were not influenza. Dilution of the group of clinical influenzas with illness due to other causes probably took place, because, even in the control group, only two-thirds of illnesses so diagnosed were confirmed serologically, whereas the methods used might be expected to confirm 80 to 90% of cases of virus influenza. Alternatively, serological tests may be less able to detect evidence of influenza virus infection in vaccinated than in unvaccinated persons.

The antibody rise resulting from a single injection of influenza virus vaccine into adults is probably not a primary response, since most adults would previously have encountered a closely related antigen as the result of natural infection with the virus. The raised level of H.I. antibody observed after immunization is generally accepted as an indication of reduced susceptibility to infection; but if infection does occur in persons exhibiting this secondary response it may not be capable of provoking a further fourfold rise in antibody titre.

The level of H.I. antibody in acute-stage sera was considerably higher in the trial group than in the control group, the difference between geometric mean titres being approximately fivefold when the current 1953 virus strain was used as antigen and tenfold when the strains present in the vaccine were used. Further evidence of this difference is shown in Table III, where it may be seen that 33 out of 34 acute-stage sera from controls had a H.I. titre to the 1953 virus strain of less than 1/10, whereas 20 out of 28 acute stage sera from those who had received the trial vaccine were 1/10 or higher. Sixteen out of 17 volunteers found positive by this test had an initial titre of less than 1/10, and that of the remaining positive case was 1/10. H.I. tests using the other two virus strains as antigen gave very similar results. Comparison of findings on acute- and convalescent-stage sera by the same tests showed that the acute-stage antibody levels in the trial group were approximately equal to those found in the convalescent stage in the controls. Thus the vaccine provoked antibody levels of the same order as those resulting from natural infection. Though one conclusion is that persons with an antibody titre above a given level are not susceptible to infection, it may also be that serological tests are less able to detect it when it occurs.

TABLE III.—*Serological Diagnoses of Influenza in Relation to Antibody Level in Acute-stage Sera (Based on Haemagglutination-inhibition Tests Using a 1953 Virus A Strain as Antigen)*

Antibody Level in Acute-Stage Sera	Trial Group		Control Group	
	No. of Illnesses	No. Positive	No. of Illnesses	No. Positive
Titre less than 1/10	8	3	33	13
„ 1/10 or higher	20	1	1	0
Total No. tested ..	28	4	34	13

Wiener, Henle, and Henle (1946) observed that a rise in antibody to soluble antigen was detected only occasionally with the batches of vaccine they were using. Kirber and Henle (1950) later suggested that the soluble antigen complement-fixation test should therefore be of value for the diagnosis of influenza in a recently vaccinated population. We were unable to confirm that injection with the vaccine used failed to cause an increase in antibody to soluble antigen. Table IV shows antibody levels to soluble antigen in acute-stage sera taken from volunteers in control and trial groups, and in convalescent sera from the 16 cases

TABLE IV.—*Distribution of Antibody Titres to Influenza Virus A Soluble Antigen*

	No. of Sera having Titres of:					Total Sera	Percentage 1/2 or Less	Percentage 1/8 or More
	1/2 or Less	1/4	1/8	1/16	1/32			
Trial group: Acute-stage sera	0	8	15	5	0	28	*0*	*71*
Control group: Acute-stage sera	19	7	6	1	1	34	*56*	*24*
Convalescent sera from confirmed cases of influenza A ..	0	4	5	7	0	16	*0*	*75*

confirmed as influenza A by at least one serological test in the control group. In the control group 56% of acute-stage sera had titres of 1/2 or less, whereas in the trial group all had a titre of at least 1/4, and 71% had a titre of 1/8 or higher. Furthermore, as was found with the H.I. tests, the distribution of titres of acute-stage sera in the trial group was very similar to that for convalescent sera from the confirmed cases of influenza A in the control group. Titres to influenza B soluble antigen did not differ in the control and trial groups, which suggests that the differences with influenza A soluble antigen were due to specific antibody. It seems improbable, therefore, that the soluble antigen complement-fixation test has any advantage over the H.I. test for the diagnosis of influenza in persons recently vaccinated with vaccine of the type used in this trial.

The main disadvantage of using clinical methods unaided by laboratory tests in the assessment of an influenza vaccine is that the proportion of illnesses correctly diagnosed as influenza is unknown, and so the degree of protection conferred cannot be determined. If the proportion of cases of true influenza to the total number of clinically diagnosed cases is low the resulting dilution may obscure the protective effect even of a good vaccine. This is particularly undesirable in the experimental stages of the development of a vaccine, when quite small differences may have considerable significance. However, it is essential that a trial method should be free from observer bias, and the clinical method in a well-designed trial has this virtue, whereas the serological method is open to question. Unless it can be shown that the chance of obtaining a detectable fourfold rise in antibody following natural infection is unrelated to the initial antibody level it would appear unwise to rely on serological methods only in any estimate of protection.

Perhaps the most important contribution which the laboratory can make to the precision of a large-scale field trial at the present time is in determining the duration and type of any influenza outbreak in communities in which the inoculated volunteers live or work. Periods in which there is no detectable virus influenza can then be excluded from the final analysis. Furthermore, knowledge of the proportion of influenzal to non-influenzal illnesses in the control group during the epidemic period would help in the interpretation of protection rates calculated from clinical diagnoses alone.

Summary

In a small-scale influenza vaccine trial undertaken mainly to determine the practicability of a trial method using both clinical and laboratory tests in the diagnosis of influenza, results led to the conclusion that the assessment of a vaccine on purely clinical grounds might understate the degree of protection, whereas one based on serological findings might exaggerate it. Possible reasons for this difference are discussed. It is concluded that, until it is shown that serological methods are able to detect cases of influenza equally well in persons who have received an influenza vaccine and in those who have not, serological diagnosis should not be the only method of diagnosis used in a vaccine field trial. In a clinical assessment the fullest use should be made of laboratory evidence to define the epidemic period in the communities concerned and to estimate the proportion of illness in the control group due to influenza virus infection. This information would enable dilution of the figures by non-influenzal illness to be reduced and should allow a more accurate assessment of the vaccine to be made.

We should like to thank the management of Vauxhall Motors Ltd. for giving facilities for this trial, and their employees who volunteered to be immunized and who tolerated blood and other tests with such good humour. We are especially grateful to the firm's medical officers, Dr. A. R. Thomson and Dr. P. M. Bennett, for their great help in finding and interviewing volunteers and giving inoculations; to Mr. Humby, of the factory records department, for his daily list of absentees; and to Dr. J. H. C. Walker, Director of the Luton Public Health Laboratory, for separating sera and storing specimens. We are indebted to Dr. R. M. Dykes, Medical Officer of Health, Borough of Luton, for his help and encouragement in the organization of this investigation.

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A FOLLOW-UP TUBERCULIN SURVEY IN THE RHONDDA FACH

BY

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Tuberculin-testing of the school population of the Rhondda Fach was first undertaken in 1950–1 as an integral part of the total community *x*-ray survey carried out in this mining valley during that period (Cochrane *et al.*, 1952). The object of the first survey was to ascertain the prevalence of cases of pulmonary tuberculosis in the valley, whether already known or as yet undiscovered, and to isolate and treat all active and infectious cases. The object of the second survey was to determine the effect of the first survey on the tuberculosis situation in the valley (Cochrane *et al.*, 1955). It was thought that tuberculin-testing of the school population should provide evidence on the existing degree of total tuberculous infectivity in 1950–1 and that retesting in 1953 might reflect changes in this situation resulting from the efforts made during the first *x*-ray survey of the valley. A sample of schoolchildren in another "control" valley were also tested in 1951, and a similar sample of children from the same schools were retested in 1954. This retesting has been combined with a follow-up study of children who were tuberculin-tested on both occasions, in the hope that a determination of the conversion and reversion rates in the two valleys might be compared.

Method of Testing

In order that the results of tuberculin-testing in 1953–4 should be comparable with those obtained in 1950–1, the same Mantoux technique was employed on both occasions—namely, 0.1 ml. of a 1/10,000 dilution of standardized O.T.—that is, 1 T.U.—was injected intradermally, and all negative reactors were retested with 0.1 ml. of a 1/100 dilution—that is, 100 T.U. The criterion adopted for the reading of these tests was that any reaction producing less than 5 mm. of induration, read at 48 hours after the injection, was regarded as negative. I administered and read the tests, as

it had been previously ascertained that no appreciable error was likely to arise through the qualitative reading of the tests by one experienced observer. Strong circumstantial evidence has also been presented, showing that the presence of bovine infection in the Rhondda Fach is unlikely to affect the results of a tuberculin survey as an index of total communal infection from human pulmonary sources (Jarman, 1953).

Results

Fig. 1 shows the results of tuberculin-testing in the Rhondda Fach in 1950–1 and in 1953. This figure is based on the testing of 2,828 children out of 4,265 over the age of 5 at school in 1950–1, and on the testing of 3,195 out of 4,614 over the age of 5 at school in 1953. The detailed numbers of children tested at various ages and the stages at which lapses occurred are shown in Table 1 (*a*) and (*b*). It has to be noted that neither the tuberculin-testing curve nor the actual numbers shown in Table I correspond exactly to the previously published results for the tuberculin-testing done in 1950–1. The reason for this is that the present curves are based on ages calculated from year of birth, whereas the curve and numbers as previously published were based on the actual age of the children as given at the time of testing. Furthermore, the school population was not defined in the first survey as it has been for the re-survey. In the first survey all children attending schools in the Rhondda Fach were included in the study; in the second survey only those children were included who attended schools in the Rhondda Fach and lived in the defined area.

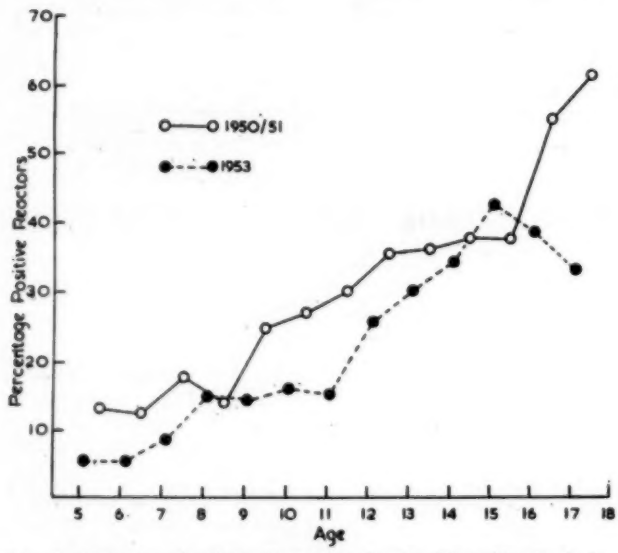

FIG. 1.—Results of tuberculin-testing in the Rhondda Fach in 1950–1 and 1953.

TABLE I.—*Results of Tuberculin-test of Schoolchildren*, 1950–1 *and* 1953

Age in Years	Total of All Children	At School	Mantoux Lapses	No. Tested	Mantoux +	% Positive
			(*a*) 1950–1			
5	386	384	143	241	31	12·9
6	405	403	133	270	34	12·6
7	407	407	107	300	53	17·7
8	391	390	95	295	41	13·9
9	386	386	112	274	67	24·5
10	398	397	122	275	74	26·9
11	379	377	87	290	87	30·0
12	420	419	132	287	102	35·5
13	375	364	151	213	77	36·2
14	443	423	168	255	97	38·0
15	435	191	120	71	27	38·0
16	404	91	55	36	20	55·6
17	383	33	12	21	13	61·9
Totals	5,212	4,265	1,437	2,828	723	25·6
			(*b*) 1953			
5	451	448	142	306	16	5·2
6	496	493	145	348	18	5·2
7	516	515	119	396	33	8·3
8	378	378	77	301	45	15·0
9	396	395	91	304	44	14·5
10	403	401	86	315	50	15·9
11	385	382	95	287	44	15·3
12	386	383	126	257	66	25·7
13	386	385	133	252	76	30·2
14	370	360	148	212	73	34·4
15	405	310	167	143	61	42·7
16	371	88	47	41	16	39·0
17	419	76	43	33	11	33·3
Totals	5,362	4,614	1,419	3,195	553	17·3

Fig. 2 shows the results of tuberculin-testing in the "control" valley in 1951 and retesting in 1954. Detailed numbers of the children tested at different age groups are given in

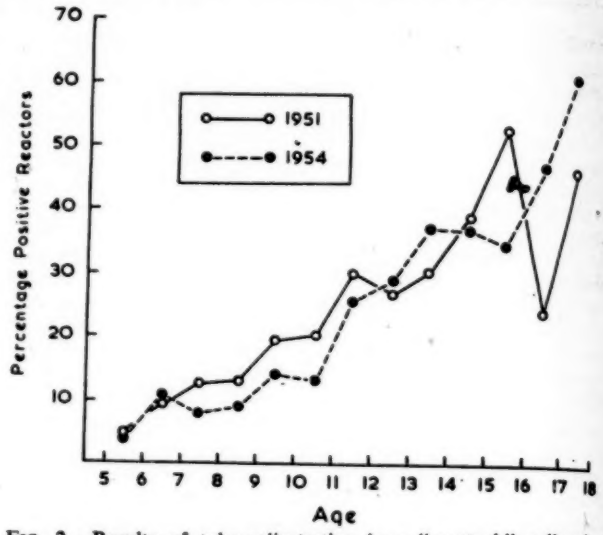

FIG. 2.—Results of tuberculin-testing in a "control" valley in 1951 and 1954.

TABLE II.—*Results of Tuberculin-testing in "Control" Valley*, 1951 *and* 1954

Age in Years	No. Tested	No. Positive	% Positive
	(*a*) 1951		
5	96	4	4·2
6	83	8	9·6
7	112	14	12·5
8	115	15	13·0
9	104	20	19·2
10	139	28	20·1
11	179	53	29·6
12	232	62	26·7
13	225	68	30·2
14	203	79	38·9
15	111	58	52·3
16	58	14	24·1
17	26	12	46·2
Totals ..	1,683	435	25·8
	(*b*) 1954		
5	82	4	3·7
6	66	6	10·6
7	79	6	7·6
8	79	7	9·7
9	93	13	14·0
10	84	11	13·1
11	117	29	25·6
12	252	72	29·0
13	252	93	36·9
14	248	90	36·7
15	119	41	34·5
16	64	30	46·9
17	41	25	61·0
Totals ..	1,576	427	27·0

TABLE III.—*Standardized Percentage of Positive Tuberculin Reactors in the Four Surveys, Based on the Results for Children Aged 5 to 14 Inclusive*

Survey	1st in R.F.	2nd in R.F.	1st in Control Valley	2nd in Control Valley
Standardized percentage positive..	24·6	18·4	20·2	18·2

Table II (*a*) and (*b*). Table III shows the standardized percentage of positive tuberculin reactors, aged 5 to 14, in the four surveys—that is, the original and follow-up surveys in the Rhondda Fach and the original and follow-up surveys in the control valley. Further reference is made to this table in the discussion.

Follow-up of Children Tested in 1950–1 and Retested in 1953–4

It was possible to follow up a fairly large sample of those tested in 1950–1 and to retest them in 1953 and 1954 in the Rhondda Fach and the control valley. Tables IV–VII summarize the results.

Perusal of these tables shows what an extremely difficult task it is to carry out, without an enormous lapse rate, a follow-up type of study which involves a procedure such as tuberculin-testing. In order to keep the tables as simple as possible the sources of the progressively increasing lapse affecting the school populations originally tested in 1950–1 have not been shown.* This lapse rate derives from children leaving school, leaving the area, and failing to complete the tests in the second survey.

It is evident from Tables IV–VII that a very small percentage of the children in the higher age groups were tested on both occasions. A pilot attempt to overcome this was made by sending a circular letter to the homes of a sample of those children who had left school but who still lived in the valley, explaining the importance of testing them a second time and offering them appointments for this purpose every evening for two weeks between the hours of 5 and 9 o'clock. The response was so poor—less than 5% of those circularized attended for the initial test, and many of those who did turn up failed to attend for the reading of the test—that an extended attempt to defeat the lapse problem in school-leavers was abandoned.

*Detailed figures relating to these lapses and the stages at which they occurred can be supplied by the author.

TABLE IV.—*Tuberculin-testing of Schoolchildren—Rhondda Fach. Follow-up of Those Mantoux-negative in* 1950–1

Age in 1951	No. Negative 1950–1	No. Tested in Both Surveys	No. Converted Negative to Positive	% Conversion
4–	908	697	37	5·3
8–	865	571	42	7·4
12–15	523	124	8	6·4
Totals	2,296	1,392 (65%)	87	6·1

TABLE V.—*Tuberculin-testing of Schoolchildren—Rhondda Fach. Follow-up of Those Mantoux-positive in* 1950–1

Age in 1951	No. Positive 1950–1	No. Tested in Both Surveys	No. Reverted Positive to Negative	% Reversion
4–	131	94	18	19·1
8–	269	181	27	14·9
12–15	303	82	3	3·7
Totals	703	357 (50%)	48	13·4

TABLE VI.—*Skin-testing Results in Schoolchildren—Control Valley. Follow-up of Those Negative at Time of First Survey*

Age in 1951	No. Negative First Survey	No. Tested in Both Surveys	No. Converted Negative to Positive	% Conversion
4–	285	162	6	3·7
8–	561	291	28	9·1
12–15	308	93	6	6·3
Totals	1,154	546 (47·3%)	40	7·3

TABLE VII.—*Skin-testing Results in Schoolchildren—Control Valley,* 1954. *Follow-up of Those Positive at Time of First Survey*

Age in 1951	No. Positive First Survey	No. Tested in Both Surveys	No. Reverted Positive to Negative	% Reversion
4–	31	20	1	5·0
8–	159	88	2	2·3
12–15	220	69	1	1·4
Totals	410	177 (43·1%)	4	2·2

When the follow-up results from these two valleys are compared it will be seen that in the Rhondda Fach 65% of those between the ages of 4 and 15 who were Mantoux-negative in 1950–1 were retested in 1953 and 6% had converted from negative to positive. In the control valley 47% of those Mantoux-negative in the same age group in 1951 were retested in 1954 and 7% had converted. There appears, therefore, to be little difference in the overall conversion rate, as actually observed by follow-up and retesting, between the two valleys. Of those in this age group who were Mantoux-positive in the Rhondda Fach, however, 50% were retested and 13% had reverted to Mantoux-negative in 1953. In the control valley 43% of those Mantoux-positive in 1951 in this age group were retested, but only 2% had reverted to negative.

X-ray Follow-up of Schoolchildren who were Mantoux-tested and X-rayed in 1950–1, and X-rayed Again in 1953

Another follow-up study of interest was possible—namely, an *x*-ray follow-up of three groups of children—those who failed to have their tuberculin tests in 1950–1 but who were *x*-rayed and found to be radiologically free from tuberculosis; those who were Mantoux-negative and *x*-ray negative in 1950–1; and those who were Mantoux-positive and *x*-ray negative in 1950–1. The results of radiological examination of these three groups in 1953 are shown in Table VIII.

TABLE VIII.—*X-ray Follow-up of Schoolchildren*

Age 1/1/51	No.	No. X-rayed in 1953	Radiological Attacks of P.T.					Morbidity		
			None	Adult Type		Prim. Type		Observation Years	Cases	Annual Rate/1,000
				− ve	+ ve	− ve	+ ve			
(a) Mantoux Positive but X-ray Negative, 1950–1										
Under 5	20	18	18	—	—	—	—			
5– ..	223	208	206	—	—	1	1			
10– ..	426	397	393	—	3	—	1	1,640	7	4·3
15+ ..	63	33	32	1	—	—	—			
Totals	732	656	649	1	3	1	2			
(b) Mantoux-Negative and X-ray Negative, 1950–1										
Under 5	340	313	312	—	—	1	—			
5– ..	1,138	1,091	1,089	—	—	—	2			
10– ..	879	825	821	3	1	—	—	5,720	8	1·4
15+ ..	69	59	58	1	—	—	—			
Totals	2,426	2,288	2,280	4	1	1	2			
(c) Mantoux Lapses but X-ray Negative, 1950–1										
Under 5	303	286	286	—	—	—	—			
5– ..	456	427	427	—	—	—	—			
10– ..	547	497	496	1	—	—	—	3,340	2	0·6
15+ ..	158	126	125	—	—	—	1			
Totals	1,464	1,336	1,334	1	—	—	1			

Of the 656 children who were Mantoux-positive in 1950–1, 7 (1.1%) showed radiological evidence of pulmonary tuberculosis in 1953. Out of 2,288 who were Mantoux-negative in 1950–1, 8 (0.35%) showed radiological evidence of pulmonary tuberculosis in 1953. This is in rather unexpected contrast to those who were Mantoux-positive in 1950–1. Out of 1,336 children who failed to have their tuberculin tests in 1950–1 only 2 developed radiological pulmonary tuberculosis in 1953.

Discussion

The crude results of tuberculin-testing in a community free from bovine infection presumably reflect the degree to which sources of human infection—that is, total tuberculous

infectivity—exist in that community. Changes in the percentage of positive reactors at various age groups from year to year reflect changes in two processes occurring concurrently—namely, the rate of conversion from tuberculin-negative to tuberculin-positive, and the rate of reversion from tuberculin-positive to tuberculin-negative. The factors influencing Mantoux conversion have been widely and exhaustively discussed in the literature, but those affecting the waning and loss of tuberculin sensitization—that is, Mantoux reversion—have been less explored.

This subject is discussed, however, in considerable detail in the Prophit Tuberculosis Survey (Daniels *et al.*, 1948). The evidence presented in this admirable follow-up study suggests that loss of sensitivity and Mantoux reversion occurs least often in those groups with the highest degree of exposure; and the authors conclude, in respect of the evidence they present in their survey study, that "desensitization appears to be inversely related to exposure, to a degree that renders improbable any serious error by false reactions." On the other hand, the same factors affect the conversion rate in the opposite direction—namely, that Mantoux conversion occurs most frequently in those groups with the highest degree of exposure.

When the crude results of tuberculin-testing in the Rhondda Fach and the control valley are compared it would appear that there has been a definite decline in the general level of tuberculin sensitization amongst the children tested in the Rhondda Fach, but that the decline in the control valley (Figs. 1 and 2) is of a less degree.

The comparison between actually observed conversion and reversion rates in the two valleys (Tables IV–VII) is of great interest, but the interpretation of the differences observed is beset with difficulties.

It will be noted that the conversion rates are similar in the two valleys, though the rate for the control valley is based on the retesting of only 47.3% of those negative in the first survey. When the reversion rates in the two valleys are compared it will be seen that, out of a 50% sample of those positive in 1950–1 who were retested in the Rhondda Fach, 13.4% had reverted to negative, whereas in the control valley out of a 43% sample of those positive in 1951 only 2.2% had reverted to negative.

The results of the prevalence of positive reactors at different ages and the data on conversion and reversion have been subjected to statistical analysis by Mr. R. G. Carpenter (University of Cambridge, Department of Human Ecology and University Health Service). In this analysis adjustments have been made for the difference in the period of time elapsing between the Rhondda Fach surveys and the two surveys in the control valley. When the percentage positive at each of the four surveys is standardized, the standardized rates (Table III) suggest that there is a small reduction of the number of positives in the control valley and a larger reduction in the Rhondda Fach. These rates are derived in a similar way to standardized death rates. Analysis confirms that the reduction in the Rhondda Fach is unlikely to be due to chance, while in the control valley it may be. Analysis also shows that the reduction in the Rhondda Fach is larger than in the control valley.

A similar analysis has been made of the conversion and reversion rates and a significance test has been carried out. The difference in the reversion rates for all ages taken together for the Rhondda Fach and the control valley appears to be just significant.

The statistical analysis of these results rests on the assumption that the sampling from the population is random. This cannot be asserted, as it is well known that sampling can be regarded as random only if it is definitely made so. However, all four surveys were carried out in much the same way—that is, on children in schools whose parents consented. It would therefore seem reasonable to suppose that the results of the statistical analysis are correct even with the small proportions and numbers of persons actually followed up. Though the data on conversion and reversion rates should be regarded with caution, it would seem that a higher reversion rate rather than a lower conversion rate may be the main cause of the decline of the number of positive reactors in the Rhondda Fach, as compared with the control valley.

It should be mentioned that, though no detailed study has been done in relation to environmental factors and population density, the two valleys are typical mining valleys in the South Wales coalfield and would appear to be reasonably comparable in respect of these factors.

An unusual and unexpected finding is that shown in Table VIII. The morbidity rate in children originally Mantoux-negative and *x*-ray negative is 1.4, whereas the rate in children originally Mantoux-positive and *x*-ray negative is 4.3. The literature relative to this subject was extensively reviewed in the Prophit Survey (Daniels *et al.*, 1948), and almost all observers had demonstrated that the radiological attack rate was higher among those previously negative than in those Mantoux-positive. This was one of the main conclusions drawn in the Prophit Report. Three American observers reported findings which were not in accord with this (Myers and Harrington, 1934; Pope *et al.*, 1939; Stewart, 1940). These authors attributed these contrary findings to the very low degree of tuberculous infectivity in those areas in America from which these observations derived.

It can be reasonably argued that where tuberculous infectivity is very low new cases could arise as the result of delayed radiological manifestations in those already infected—that is, in Mantoux-positives—at an equal or even higher rate than the occurrence of similar manifestations in those not yet infected at all—that is, in Mantoux-negatives.

More recently Palmer and Shaw (1953), in following up 282,000 children and others, some of whom had B.C.G. and others not, found that by far the greatest proportion of new cases of tuberculosis occurred among those who had originally been Mantoux-positive.

It should be noted, however, that these originally Mantoux-positive cases were not classified radiologically. Nevertheless, the investigations being conducted by the American Public Health Service are worthy of the closest study, because three of them—those amongst the American Indian schoolchildren, Puerto Rican children, and Ohio mental patients—involve communities where tuberculous infectivity is likely to be high rather than low.

Summary

Schoolchildren in the Rhondda Fach and in a "control" valley were tuberculin-tested in 1950–1 and again in 1953–4.

A follow-up study on those tested in 1950–1 and retested in 1953–4 was carried out. The large "lapse" rate involved, especially in the higher age groups, reveals how difficult a follow-up study of this kind, involving a procedure such as tuberculin-testing, is among schoolchildren.

The crude results of tuberculin-testing on both occasions suggest that there has been a fall in tuberculin sensitization of the schoolchildren in the Rhondda Fach which is not revealed to the same extent in the results of retesting in the control valley. Statistical analysis shows that the fall in percentage found positive in the Rhondda Fach is unlikely to be due to chance, whereas in the control valley it may be.

The actually observed overall conversion rate for the period between the surveys is 6.1% for the Rhondda Fach and 7.3% for the control valley. The observed reversion rate is 13.4% for the Rhondda Fach and 2.2% for the control valley.

Expressed as annual rates these are: 2.4% and 2.4% for conversion and 5.4% and 0.7% for reversion,

respectively. Statistical analysis shows that the difference between reversion rates in the Rhondda Fach and those in the control valley is significant.

The morbidity rates amongst the schoolchildren originally tested in the Rhondda Fach in 1950–1 are 0.6 for those who were "lapses" for Mantoux-testing in 1950–1; 1.4 for those Mantoux-negative in 1950–1; and 4.3 for those Mantoux-positive in 1950–1. This is an unusual finding, and might possibly be related to reduction of tuberculous infectivity in the valley.

My thanks are due to Mr. John H. Phillips, administrative officer of the Mass Radiography Service, who organized the survey, to Mr. R. G. Carpenter, who was responsible for statistical analysis of the material, and to Professor F. R. G. Heaf, Dr. A. L. Cochrane, and Mr. P. Oldham for advice and criticism.

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INVESTIGATION AND TREATMENT OF SEPTIC ABORTION

BY

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With the advent of penicillin the treatment of puerperal infections underwent a profound revolution. Post-partum puerperal sepsis has now ceased to be a serious problem, and can usually be treated without removal of the patient to a special puerperal sepsis unit. Post-abortum sepsis, on the other hand, still presents diagnostic and therapeutic problems, and it is the purpose of this paper to review these in the light of our experiences of the past five years. This department may claim to be in a unique position to conduct such a review, as it is primarily intended for the treatment of septic cases.

Classification

A fundamental difficulty in the classification of cases of septic abortion arises from the fact that the uterus is not necessarily involved in the infective process. We have therefore classified the 995 cases occurring in the period under review into the following three groups:

Group 1.—Those with complete or incomplete abortion without uterine infection (421 cases).

Group 2.—Those with local uterine infection (482 cases).

Group 3.—Those with spread of infection to the uterine appendages, peritoneum, blood stream, or viscera (92 cases).

Criteria of Uterine Sepsis

The common criteria of uterine sepsis comprise: (1) general signs of infection, of which pyrexia and tachycardia are the most important; (2) local signs such as tenderness and subinvolution of the uterus and alterations in the lochia; and (3) bacteriological and haematological findings. In our experience none of these are in themselves indisputable evidence of uterine infection. All may be present with infected retained products of conception, and often only after evacuation of the latter can a definite assessment be made. We estimate the relative reliability of these individual criteria as follows.

Pyrexia

Elevation of temperature is traditionally regarded, in Britain at least, as the most reliable general sign of infection, and provides the basis of the definition of the notifiable state of puerperal pyrexia. During the period under review a change was made in this definition, presumably to conform with changing conditions and the ever-increasing emphasis laid upon the need for prompt notification and treatment. Whereas prior to August 1, 1951, the notification of puerperal pyrexia required that, in patients within 21 days of childbirth or miscarriage, a temperature of 100.4° F. (38° C.) should have been maintained for 24 hours or have recurred during that period, subsequent to that date it has been sufficient grounds for notification that the patient, within 14 days of childbirth or miscarriage, should have developed a temperature of 100.4° F. (38° C.). This elimination of the 24-hour qualifying period had the effect of trebling the number of notifiable cases in England and Wales per week, but gave even less indication than before of the incidence of true uterine infection. Attention has already been drawn to the present unsatisfactory position (Gordon, 1951; Calman and Gibson, 1953).

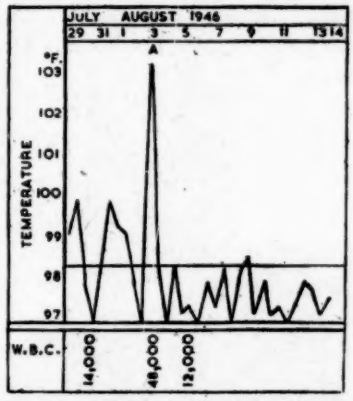

FIG. 1.—Inevitable abortion. Negative cultures from cervix, urine, and blood. Pyrexial until the day of abortion (August 3, 1946), and leucocytosis increased to 48,000 on that day. Immediate and uneventful recovery without chemotherapy.

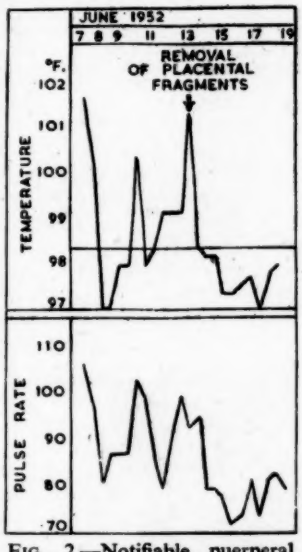

FIG. 2.—Notifiable puerperal pyrexia accompanying incomplete abortion. No evidence of uterine sepsis. Persistent pyrexia until retained products were removed. Then uneventful recovery without chemotherapy.

Our experience has shown that both inevitable and incomplete abortions may be accompanied by considerable degrees of pyrexia without demonstrable uterine infection. Fig. 1 shows the chart of a case of inevitable abortion in which not only a temperature of 103° F. (39.4° C.) but also a leucocytosis of 48,000 occurred; yet bacteriological examination was negative, and, following the spontaneous expulsion of the uterine contents, recovery was immediate and uneventful without chemotherapy.

Similarly, many cases of incomplete abortion show degrees of pyrexia which render them notifiable, but in which either spontaneous or assisted evacuation of the uterine contents

brings about uneventful resolution. Fig. 2 shows such a case in which chemotherapy was not required. While it may certainly be held that such cases are septic, since organisms are proliferating in the necrotic retained products of conception, they present no evidence of infection of the uterus. The immediate and uneventful resolution of pyrexia after emptying of the uterus supports this view. Moreover, it tends to be overlooked that the degree of pyrexia does not necessarily vary in direct ratio with the severity of the infection; indeed, cases of severe spreading generalized peritonitis may be accompanied by a low-grade pyrexia which does not even attain the level of notifiability. Two such cases are shown in Figs. 3 and 4. It is clear, therefore, that the selection of an arbitrary level of pyrexia as a criterion for notification is inherently unsound, and we agree with Calman and Gibson (1953) that it might well be abandoned. As from March 1, 1955, however, practitioners have been requested to state the probable cause of the pyrexia. While this is a step in the right direction, the only basis of notification of any value from an epidemiological standpoint is that of uterine infection.

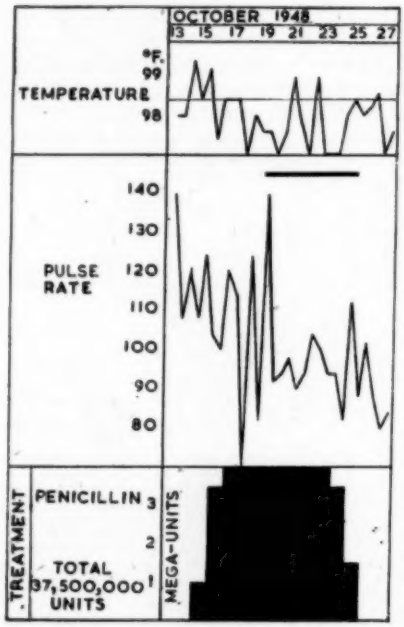

FIG. 3.—Severe *Cl. welchii* peritonitis complicated by complete ileus. Pulse rate a more delicate criterion of progress of infection than temperature. Temperature never reached the level of notifiability.

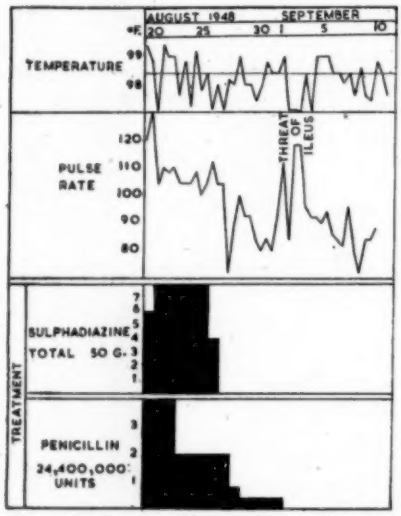

FIG. 4.—Severe *Cl. welchii* peritonitis. Threat of ileus on September 3, 1948, reflected in the pulse rate but not in the temperature, which did not reach the level of notifiability.

Tachycardia

The unreliability of the temperature as an indication of infection impelled us to pay more attention to the pulse rate, and we have found this to be a more sensitive guide to the progress of infection. In the case shown in Fig. 3 the improvement attendant upon measures adopted to combat complete paralytic ileus is reflected at once in the steadying of the pulse. In the case shown in Fig. 4 threatened ileus was accompanied by a rise in the pulse rate. In neither case does the temperature chart give any clue to these developments. In spreading infections we have found that the pulse rate is invariably rapid, usually above 110; the temperature, on the other hand, shows a wide range of variability, but, in severe post-abortum sepsis at least, is often low-grade.

Tenderness of Uterus

After passage of the foetus, tenderness of the uterus is a fairly reliable sign of infection. When tenderness is present over the lower abdomen and is accompanied by a positive release sign and a rapid pulse, a spreading infection with involvement of the peritoneum should be assumed. In threatened abortions, however, there may be extreme tenderness over the lower abdomen and a positive release sign may be obtained without infection being present. A uterus which is contracting in an attempt to expel the foetus and/or placental fragments can be extremely tender if the os is closed or rigid, and, contrary to what is often stated in textbooks, this is by no means an uncommon phenomenon. The rapidity with which both tenderness and the positive release sign disappear after expulsion of the uterine contents suggests that the signs may result from the powerful contraction of unstriped muscle. A similar condition may be demonstrated with a distended bladder.

Subinvolution of Uterus

Provided the uterus is empty, subinvolution may be taken as a certain sign of infection. So unreliable are the histories relating to duration of pregnancy in abortion cases, and so difficult may it be with a closed os to determine if an abortion is complete, that the value of this sign for immediate assessment is minimized.

Alterations in Lochia

In the absence of any history of chronic vaginal discharge frankly purulent, or even mucopurulent, lochia are valuable evidence of sepsis. Offensive lochia point to infection with bowel-derived organisms, which are the commonest pathogens in abortion cases.

Bacteriological Evidence of Infection

The organisms most commonly found in puerperal infections may be classified as follows: (1) Haemolytic streptococci of Lancefield Group A, which are invariably pathogenic and the presence of which on cervical culture is in itself indicative of infection. (2) Haemolytic streptococci of Lancefield groups other than A, non-haemolytic streptococci (mainly *Streptococcus faecalis* or *enterococcus*), coliforms, the two groups of anaerobes—the sporing type represented by *Cl. welchii*, the non-sporing type by the anaerobic streptococcus—and coagulase-positive staphylococci. These are usually saprophytes but are potential pathogens. The staphylococcus, though small in incidence in this particular series, is particularly apt to produce serious complications when it has become invasive. (3) Coagulase-negative staphylococci and diphtheroids. These are purely commensals and we classify them as negative cultures.

Table I shows the incidence of positive cultures in the three main groups. Positive cultures were found in 89.4% of cases with local uterine sepsis, while cases without uterine infection had only 74% positive cultures. The rapid inward spread of the organism probably accounts for the fact that cases with invasive complications showed only 80.5% positive cultures.

TABLE I.—995 *Cases Showing Incidence of Positive Cultures in the Three Main Groups*

Group 1		Group 2		Group 3	
Cases	Positive	Cases	Positive	Cases	Positive
421	312 (74%)	482	432 (89·4%)	92	74 (80·5%)

The incidence of the six organisms principally concerned (and accounting for 98% of all pathogens) is shown in Table II according to their appearance in single or in mixed culture. Their overall percentage incidence in the three

main groups is shown in the form of a histogram (Fig. 5). We thus see that in post-abortum sepsis, as opposed to post-partum sepsis, (*a*) haemolytic streptococci of Lancefield Group A are seldom found; (*b*) bowel-derived organisms are most commonly found: usually saprophytic, they require favourable factors for conversion to pathogenicity; and (*c*) mixed infections are common.

TABLE II.—804 *Cases of Septic Abortion with Positive Cultures Analysed According to the Findings of Individual Organisms (a) Alone and (b) in Mixed Culture*

Group		Total No. of Cases	Total No. of Isolations	Coliforms	*Cl. welchii*	Non-haem. Streptococci	Anaerobic Streptococci	Staphylococci	Haemolytic Streptococci
1	Alone	191	191	73	18	44	41	12	3 (no group A)
	Mixed	104	219	78	33	65	36	16	1 (" " ")
2	Alone	260	260	117	27	31	30	31	24 (6 " ")
	Mixed	176	365	131	78	66	39	34	17 (1 " ")
3	Alone	45	45	20	4	11	5	0	5 (3 " ")
	Mixed	28	58	23	12	13	4	3	2 (no " ")

Of the 818 cases with positive cultures (pathogens), 14 were due to miscellaneous organisms and are not included in the above main types.

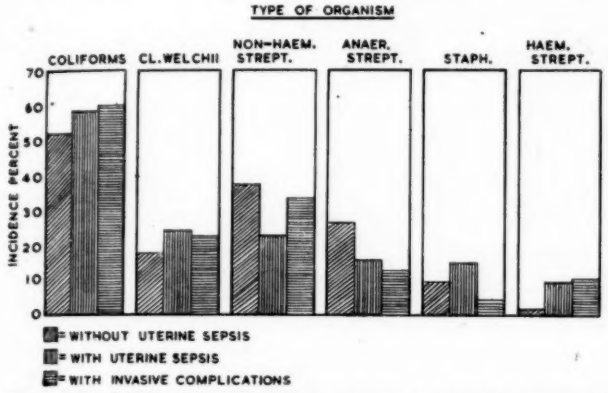

FIG. 5.—Incidence of principal organisms in the three groups.

Conversion of Saprophytic Organisms into Pathogens.—It has been previously shown that even a formidable organism like *Cl. welchii* behaves as a harmless saprophyte in most cases of post-abortum infection (Ramsay, 1949). This can be explained either by a wide variation in the toxigenicity of *Cl. welchii* strains (Butler, 1943) or on the assumption that, in common with other bowel-derived organisms, conversion to pathogenicity requires the presence of certain necessary factors. These factors would appear to be: (*a*) retention of necrotic products of conception long enough to allow of the proliferation of the common organisms introduced from the bowel; and (*b*) trauma: cases in which unskilled attempts to procure abortion have resulted in muscle injury provide particularly suitable conditions for the growth of *Cl. welchii*, which, together with coliform organisms, is most commonly associated with the spreading type of infection.

Our experience suggests that, except in the case of infection with haemolytic streptococci of Lancefield Group A, a diagnosis of infection should not be made on bacteriological findings alone.

Haematological Evidence of Infection

In Table III we show the result of the analysis of 715 cases in which a record of the white blood cell count is available. In the group without uterine infection the white blood cell count was between 10,000 and 20,000 in 107 cases (36.8%) and over 20,000 in 15 (5.4%). Haemorrhage (Whitby and Britton, 1953), trauma, and the presence of tissue autolysates from disintegrating products of conception are all factors which may contribute to these high counts. *Cl. welchii* infection is known to show higher white blood cell counts than infection in which other organisms are

TABLE III.—*Analysis of 715 Cases According to White Blood Cell Counts in the Three Groups*

Group	Less than 5,000	5,000–10,000	10,000–20,000	More than 20,000	Total
1	8	147	107	15 (5 *Cl. welchii*)	277
2	17	131	168	33 (11 *Cl. welchii*)	349
3	4	29	36	20 (6 *Cl. welchii*)	89
	29	307	311	68	715

responsible (Ramsay, 1949). In this series they were isolated from one-third of the cases with counts over 20,000. While useful in the early stages of an infection and before bacteriological results are available, the white blood cell count cannot be relied upon as independent evidence of infection in post-abortum cases, and is of value only when taken in conjunction with physical signs.

Management of Septic Abortion

The management of a case of abortion depends, firstly, on the stage at which it is seen, and, secondly, on the presence of factors such as haemorrhage and infection. Occasional cases of threatened abortion or even of ruptured ectopic gestation are admitted with a diagnosis of septic abortion. In the scope of this review, however, we propose to deal only with the management of the three groups of cases already described.

Common to all three groups is the necessity for early pelvic examination, the taking of cervical swabs and a catheter specimen of urine, and a haemoglobin estimation. These investigations are essential. *The necessity for investigation before therapy cannot be overemphasized, since the result of sensitivity reactions may be the all-important factor in determining the most suitable antibiotic agent; haphazard trials of the various antibiotics is not only unscientific but has, in our experience, endangered life.*

Cases with severe haemorrhage or exsanguination following prolonged haemorrhage require blood replacement. Blood grouping and cross-matching should therefore be carried out at once. The need for transfusion should be based more on the patient's general condition (in particular the state of the peripheral circulation) than upon the actual haemoglobin levels. Should immediate operation be required blood transfusion should be begun before the patient is anaesthetized. We have been impressed with the infrequency of the need for immediate evacuation. The case of septic abortion has usually ceased to bleed when admitted to hospital, and there is time for adequate blood replacement and institution of chemotherapy before surgical intervention is undertaken.

Group 1 (without uterine infection)

In this group chemotherapy is not required unless removal of retained products is thought to be necessary. Since retained products are always potentially infected we cannot confidently recommend their removal without cover of combined sulphonamide and penicillin. "Sulphatriad," 1.5 g., and penicillin, 250,000 units, are given every six hours for five days, making a total course of 30 g. of sulphatriad and 5 mega units of penicillin.

Technique of Operation.—The technique of operation has been repeatedly described by gynaecologists, and we have approximated closely to the method described by Burnett (1952) except in that, if the uterus is flabby, we find it helpful to give ergometrine, 0.5 mg. intravenously, just before the end of the operation both as a haemostatic and in order to reduce the size of the cavity, and so more accurately determine if the uterus is empty.

Group 2 (local uterine infection)

In this group the same principles apply save that all cases require the combined course of sulphonamide and penicillin.

If coliform organisms are the sole product of cervical culture, penicillin may be discontinued. Evacuation of retained products is delayed until the drugs have been given for 24 to 36 hours, although excessive haemorrhage will naturally demand immediate intervention.

Group 3 (Invasive Complications)

The primary consideration in these cases is to effect adequate control of the infection. The removal of retained products is of secondary importance except in those rare instances when persistent haemorrhage makes such a procedure imperative. In cases with a history of rigors or in which there is other evidence suggesting septicaemia, blood cultures on admission should be a part of the routine investigation.

The commonest forms of invasive complication encountered in the period under review were: (*a*) salpingitis, (*b*) parametritis, and (*c*) spreading or localized peritonitis. The large abscess in the pouch of Douglas requiring drainage by posterior colpotomy is now seldom seen. Smaller collections of pus usually resolve, but some are found to drain spontaneously per rectum or per vaginam. Laparotomy for drainage has not been required during this period. Cases of peritonitis, whether generalized or localized, were once commonly complicated by paralytic ileus. This complication is also now rarely encountered, but partial ileus may occur in cases showing tardy response to treatment.

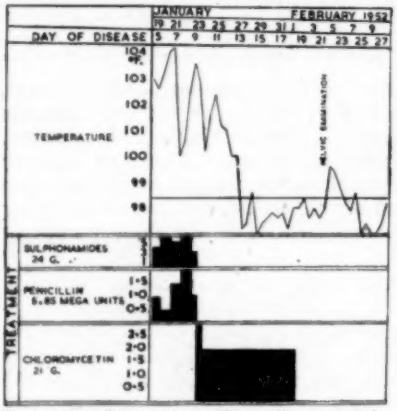

FIG. 6.—Case 1. Spreading pelvic peritonitis. Condition became worse while patient was on sulphonamide and penicillin. Responded immediately to chloramphenicol therapy.

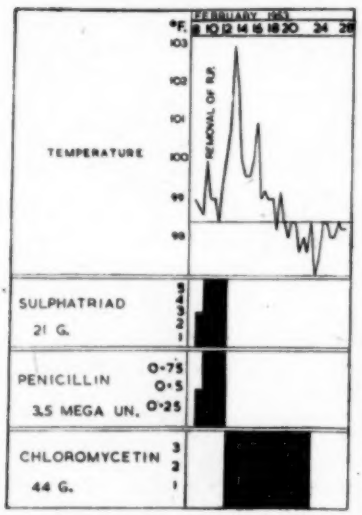

FIG. 7.—Case 2. Admitted 19 days after abortion. Cervical culture gave a growth of anaerobic streptococci and coliform bacilli. Removal of retained products under cover of sulphonamide and penicillin was followed by an exacerbation of the infective process. Chloramphenicol therapy effected rapid control.

Septicaemia is no longer a prominent complication; indeed, the most surprising and, at the same time, gratifying feature of the past five years has been the virtual disappearance of severe staphylococcal infections. In view of our previous experience with these insidious and intractable infections (Ramsay and Vahrman, 1951) and the persistence with which these organisms develop resistance to each new antibiotic, it would be too much to expect no further trouble from them. Many cases of potential septicaemia are eliminated and controlled in the early bacteriaemic phase. The rapidly developing symptoms of acute *Cl. welchii* septicaemia—jaundice, falling blood pressure, and port-wine urine—are occasionally seen, but prompt treatment with penicillin quickly arrests the infection. Only in the neglected case is a fatal issue likely to occur. *Bact. coli* bacteriaemia is a frequent feature of post-abortum infection and is commonly found after evacuation of retained products. On occasion *Bact. coli* may give rise to a fulminant septicaemia, and this was the cause of death in one of our fatal cases, in which death occurred within 24 hours of abortion and before chemotherapy had a chance to be effective.

Prompt treatment of a case of septic abortion with combined sulphonamide and penicillin controls most infections. Failure to respond usually indicates infection with coliform organisms or penicillin-resistant staphylococci. Since 1951 we have been impressed with the efficacy of chloramphenicol in this type of case, and the following case histories illustrate its value.

Case 1.—The patient whose chart is shown in Fig. 6 was admitted with spreading pelvic peritonitis. The date of abortion was not known, but she had been pyrexial with rigors for three days. After five days' treatment with combined sulphonamide and penicillin her condition was deteriorating. The abdomen was distended and lower abdominal tenderness and guarding were present. Chloramphenicol ("chloromycetin") was substituted, and a pronounced improvement was noted within 24 hours. Recovery was uneventful. The causal organism was not isolated.

Case 2.—The patient whose chart is shown in Fig. 7 was admitted 19 days after an abortion for which she had had no investigation or treatment. There was generalized lower abdominal tenderness with some distension. She had an offensive discharge, and retained products were present *in utero*, these being removed two days after admission, when adequate cover with sulphonamide and penicillin had been given. Two days later the patient complained of severe abdominal pain and became acutely distended. Cervical culture had given a growth of anaerobic streptococci and coliform bacilli. Chloramphenicol therapy was substituted for sulphonamide and penicillin, and recovery from the acute infection was thereafter uneventful.

While dramatic results must not be expected, the use of chloramphenicol or tetracycline may control infection sufficiently to permit of the adoption of general measures, such as transfusion of fresh blood, high protein intake, extra vitamins, and fresh-air balcony nursing, to reinforce the severely depleted patient's defensive mechanisms. The details of a recent case in which, at one point, surgical intervention was considered illustrate these important points.

Case 3.—This patient, whose chart is shown in Fig. 8, was admitted with genital tract infection following an induced abortion one week previously. No investigation or treatment had been carried out. Retained products were removed on the day after admission under cover of sulphonamide and penicillin. For four days the patient made good progress. Pyrexia then recurred and there was tenderness and guarding in the left iliac fossa. As coliform organisms alone had been isolated from

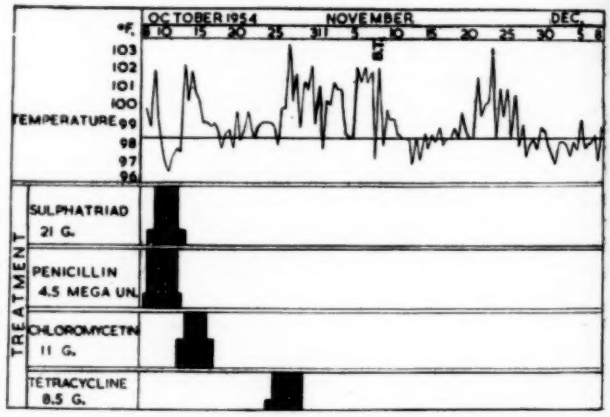

FIG. 8.—Case 3. Admitted one week after abortion. Retained products were removed under general anaesthesia on October 9, 1954. Failure of control of infection by sulphonamide and penicillin, chloramphenicol, or tetracycline. These may have helped to localize the infection. Recovery aided by general measures—for example, transfusion with fresh blood.

cervical culture a course of chloramphenicol was begun and the patient's general condition showed improvement, but extension of the pelvic mass was noted; subsequently the upper limit of this mass was defined at the level of the umbilicus. Two further exacerbations of pyrexia occurred. A course of tetracycline had no appreciable effect, and it was clear that no more could be expected from antibiotic therapy. There was a discharge of pus both per rectum and per vaginam, which probably accounted for a sudden fall of temperature on the 32nd day after admission, but this coincided also with the transfusion of 2 pints (1.1 litres) of fresh blood. Recovery was thereafter uneventful, and only a minor degree of pelvic thickening was detected at a recent examination.

Modern therapy has largely eliminated infection as a direct cause of death, and renal failure has now become the most dreaded complication of post-abortum sepsis. It was the cause of death in two of our four fatal cases; in the other two death occurred within 24 hours of admission and before chemotherapy could be effective. Bull *et al.* (1949) showed that shock, by causing ischaemia with resultant widespread damage to individual nephrons, is responsible for the renal failure. In the period under review, all cases with renal failure were also severely infected. Two types of renal damage are encountered (*Lancet*, 1954): (1) *massive renal cortical necrosis* in which the changes are irreversible and the prognosis is still hopeless; and (2) *renal tubular necrosis*. The prognosis now is relatively favourable. Limitation of fluid intake and the non-protein diet implicit in the principles of the Bull–Borst regime have made this possible. In practice we have found the fat content of the "Hammersmith cocktail" to be badly tolerated by many patients, and this may be halved without detracting from the value of the treatment. When vomiting persists to the extent of making it impossible to maintain the intake, intravenous administration of 40% glucose via the inferior vena cava has been tried (Russell *et al.*, 1954).

Summary

A review is given of 995 cases of septic abortion treated in a special puerperal sepsis unit. The relative reliability of the common general and local signs of infection in regard to the diagnosis of uterine sepsis is fully discussed.

The bacteriological features of post-abortum, in contradistinction to post-partum, sepsis, are analysed and the value of bacteriological and haematological findings is discussed.

The management of the case of septic abortion is described. The need for adequate investigation before therapy is emphasized.

The value of sound chemotherapeutic control of the infected case is reflected in a considerably reduced mortality. There were four deaths in the series: two of these were wholly attributable to acute renal failure, and in the other two chemotherapy had very little chance to be effective.

We wish to thank Dr. D. D. Reid, of the London School of Hygiene and Tropical Medicine, for his helpful advice in the compilation of the tables.

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INTESTINAL LENGTH IN MAN

BY

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Every medical student knows that the length of the small intestine is 22 ft. (6.7 m.) or thereabouts, for his textbook has taught him so. Every surgeon knows from his experience that there is great variation in intestinal length, but few realize the magnitude of this variation.

It is the aim of this paper to draw attention to the fact that the accepted measurements are averages and may be grossly misleading in any individual case, since the variation is of the order of 100%. The surgical applications of this fact are discussed. An account is given of the complications which arise when only a very short length of gut remains, and suggestions are made on their management.

Accepted Measurements

The lengths of small and large intestine quoted by well-known textbooks are given in Table I.

TABLE I

Author	Small Intestine	Large Intestine
Cunningham (1940)	Over 20 ft. (6·1 m.)	5 to 6 ft. (1·5 to 1·8 m.)
Grant (1948)	20-odd ft.	Not stated
Gray (1942)	About 6 m. (19·5 ft.)	About 1·5 m. (5 ft.)
Ross (1939)	6·75 m. (22 ft.)	180–195 cm. (70·9–76·8 in.)

These figures are stated without qualification in the books, and no hint is given to the student that great deviations from the mean are not at all uncommon.

This investigation was prompted by a chance observation made in the post-mortem room.

A woman aged 63 had been admitted to Chase Farm Hospital complaining of severe abdominal pain, diarrhoea, and the passage of blood per rectum of two weeks' duration. For the past week vomiting had been severe. The physical signs were those of intestinal obstruction, and the duty registrar had performed a laparotomy. The patient was found to have a mesenteric thrombosis which had caused a long loop of small intestine to become gangrenous. This loop was resected and side-to-side anastomosis performed between the remaining portions of small intestine. The resected portion was found to measure 8 ft. (2.4 m.). The patient did not recover from the operation, and at necropsy it was obvious that an unexpectedly short segment of gut remained. This segment measured only 3 ft. (91 cm.) from pylorus to ileo-caecal valve, allowance having been made for the overlap at the anastomosis. Apart from appendicectomy, she had had no previous operation on the gut, so her total length of small intestine was 11 ft. (3.3 m.). The shortness did not, however, extend to the large gut, as this structure measured 6 ft. (1.8 m.) from ileo-caecal valve to anal canal.

The literature was consulted and records were found of a few series of measurements. Treves, in 1885, measured the small and large intestine in 100 fresh adult bodies and found the average length of the small gut to be 22 ft. 6 in. (6.9 m.) in the male and 23 ft. 4 in. (7 m.) in the female, with extremes of 15 ft. 6 in. (4.7 m.) and 31 ft. 10 in. (9.7 m.), but he does not state the relative numbers of men and women, the ages of the women, or the percentage of subjects whose gut lengths varied greatly from the average. He concluded that the length of the bowel is independent, in the adult at least, of age, of height, and of weight; nor is the ratio between the measurements of the large and small intestine constant.

TABLE II

Author	No. of Bodies	Sex	Small Gut			Large Gut			Whole Gut		
			Min.	Aver.	Max.	Min.	Aver.	Max.	Min.	Aver.	Max.
			ft. in.	ft. in.	ft. in.	ft. in.	ft. in.	ft. in.	ft. in.	ft. in.	ft. in.
Present series (1955)	65	M	16 0	20 11	25 9	4 6	5 11	6 6	20 6	26 4	31 9
	35	F	11 0	19 5	23 6	4 6	5 2	6 0	17 0	24 2	29 6
Bryant (1924)	160	Both	10 0	20 6	28 4	3 4	5 2	10 10	13 4	25 8	39 2
	27	M	15 0	21 9	26 8	3 8	5 4	9 2	18 8	27 1	35 10
	17	F	13 4	19 3	25 0	3 4	4 6	6 8	16 8	23 9	31 8
Dreike (1894)	27	M	13 10	20 9	33 3	3 8	5 3	7 4	17 6	26 0	40 7
	23	F	11 2	17 3	28 2	3 8	5 0	6 4	14 10	22 3	34 6
Treves (1885)	100	M	15 6	22 6	31 10	3 3	4 8	6 6	18 9	27 2	38 4
		F	18 10	23 4	29 4	3 3	4 6	6 6	22 1	27 6	35 10

1 foot equals 30·48 cm.

Further series are reported from Germany by Dreike (1894) and from America by Bryant (1924). It was shown, moreover, by Lamb (1893) that there are racial differences in intestinal length, the average being higher in India than in Europe and higher still among American negroes, in whom lengths of 40 ft. (12.2 m.) are not unknown. All these measurements refer to the cadaver. In life, intestinal length is considerably less. Alvarez (1940) says: "Recent studies show that during life the whole tract from mouth to anus is usually only 8 to 10 feet long, or from 2.4 to 3 metres." Noer and Johnston (1939) published a series of cases of intestinal obstruction treated by decompression, using a tube 10–12 ft. (3–3.7 m.) long. They found the average length of tube from mouth to anus to be 9 ft. (2.7 m.). In their paper a photograph is shown of a patient with the ends of a 10-ft. (3-m.) tube protruding from both mouth and anus.

Alvarez quotes experiments performed by Van der Reis and Schembra in 1924 showing that the tube does not have the gut telescoped upon it, but lies smoothly along the mesenteric border. Loss of tone appears to be responsible for the lengthening which takes place after death.

However, it seems reasonable to assume that variation in cadaveric length reflects variations which were present in life, so it seemed worth while to repeat the observations made by Treves on subjects in this country.

Method

Measurements were made of the length of small gut from pylorus to ileo-caecal valve, and of large gut from ileo-caecal valve to anal canal, in 100 unselected adult subjects. In some cases the post-mortem examination was conducted within a few hours of death; in others the body had been kept in the refrigerator for one to three days. In no case had any preservative been used. Subjects were not included if they had had previous gut resections (other than the case already mentioned in which the resected portion had been carefully measured) or if there was gross intestinal disease which distorted the tube or made accurate measurement impossible.

The intestine was removed from the body; the mesentery and omentum were cut off close to the tube, which was kept moist in a bowl. The gut was then measured by being laid without tension against a 1 ft. (30 cm.) metal ruler. The measurements were all made by Mr. Conlon, of the morbid anatomy department, or myself. Successive measurements of the same intestine by the same observer varied by less than 2%, and observations by the two workers differed by less than 7%.

The effect of tension was investigated. After routine measurement the gut was pulled with the hands as strongly as possible without rupturing it and was then remeasured. This treatment produced an increase in length of 4% in the small gut and of 14% in the large gut.

A measured length of 30 cm. of intestine was filled with water and the loop was left to hang from its two ends for 30 minutes, so mimicking the distension of a dependent loop in intestinal obstruction. The loop was then measured full of water, as it was, and after the water had been released. The length of small intestine had increased to 31 cm. (3.3%), both full and empty, while the large gut remained 30 cm. long when full of water but stretched to 32 cm. (6.6%) after it had been emptied. These tests indicate that intestinal contents are accommodated by increase in girth rather than length.

Results

Of the 100 subjects, 65 were men aged 27–91, and 35 were women aged 33–85. The measurements of their intestines are summarized in Table II, where they are compared with figures obtained by other workers. The length of the large intestine is shown to be very much more constant than is that of the small gut. The correspondence between the figures in the four series is, on the whole, a close one, though Treves alone found a greater average length of small gut in women than in men. In the present series the average length of the small gut was 8% and that of the large gut 14% greater in men than in women.

The distribution of cases round the mean was next investigated, with the result shown in Table III. That is to say, all but approximately 14% of subjects of both sexes have

TABLE III

	Subjects with Gut Less than 85% of Average	Subjects with Gut Longer than 115% of Average
Small gut Males	5 (7·7%)	4 (6·1%)
Small gut Females	2 (5·7%)	3 (8·6%)
Large gut Males	2 (3%)	0
Large gut Females	0	4 (11%)

small-gut lengths within plus or minus 15% of the average and the number who have unusually short large intestines is very small.

Furthermore, in the present series the shortest small gut in women is 47% of the longest and 56% of the mean; in men it is 62% of the longest and 75% of the mean. The shortest large gut in women is 75% of the longest and 87% of the mean; in men it is 70% of the longest and 76% of the mean.

Treves's (1885) statements were next checked concerning the absence of correlation between bowel length and age and height of the subject.

Figs. 1, 2, and 3 confirm that there is no relation between gut length and age. Bryant stated that there was an increase of 20% in colon length and a decrease of 7% in small-gut length with age rise from 20 to 80 years. This series does not bear out that contention.

Though Treves found that gut length was independent of the height of the subject, Figs. 4, 5, and 6 show clearly that small, large, and total gut lengths are so related.

Whereas the ratio between the lengths of small and large gut is not absolutely constant, Fig. 7 shows that the small gut is three to four times as long as the large in the majority of cases.

Surgical Importance

The cases of surgical importance are obviously those in the group with the small gut abnormally short. In such patients the removal of what would in the average person be a perfectly "safe" length may leave them with a grossly inadequate absorptive surface.

The length of gut to be removed in a massive resection is seldom a matter of election, but if the surgeon realizes that he has been forced to leave a dangerously short segment of small gut he can institute appropriate treatment at once and may be able to forestall the development of serious nutritional deficiencies. It is wise, therefore, roughly to measure the length of bowel which remains after resection, rather than to infer its length after measuring the excised portion.

Haymond (1935), reviewing cases of massive resection of the gut, came to the conclusion that man can tolerate the resection of 33% of the total length of his intestine and can subsequently return to normal, but if more than 50% is removed serious metabolic disturbances occur.

There are, however, reports of some astonishing cases, such as that recorded by Shonyo and Jackson (1950). Their patient, a woman aged 41, had a resection of almost the whole of her small intestine for an adenocarcinoma of the jejunum which had involved adjacent loops. There remained only 15.3 in. (39 cm.) between the pylorus and

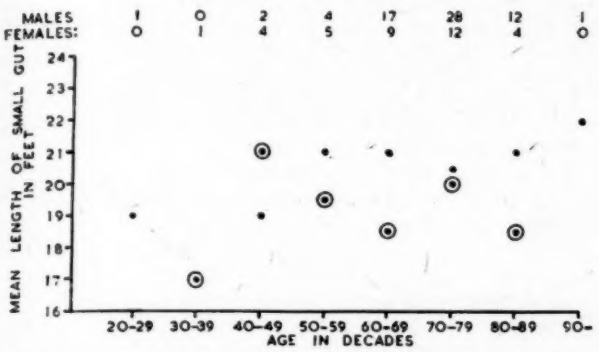

FIG. 1.—Correlation between length of small gut and age of subject. ●=Males; ⊙=females.

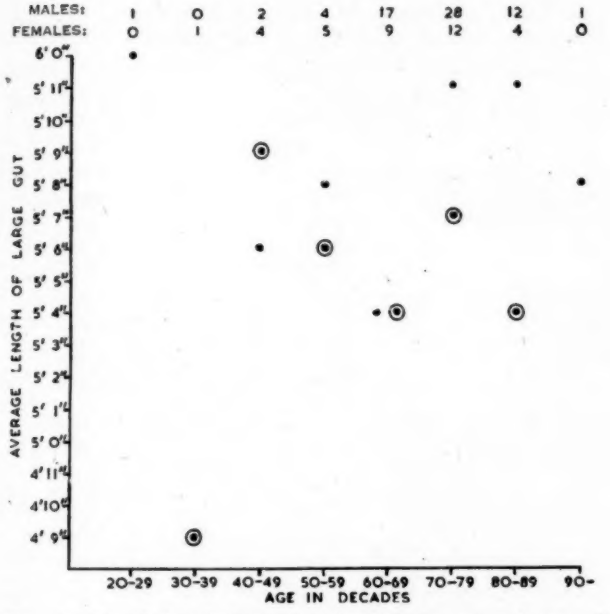

FIG. 2.—Correlation between length of large gut and age of subject. ●=Males; ⊙=females.

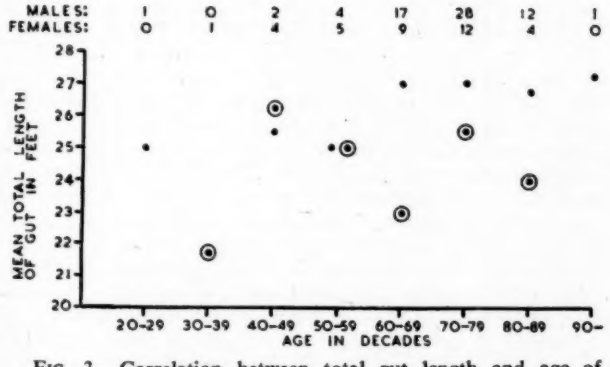

FIG. 3.—Correlation between total gut length and age of subject. ●=Males; ⊙=females.

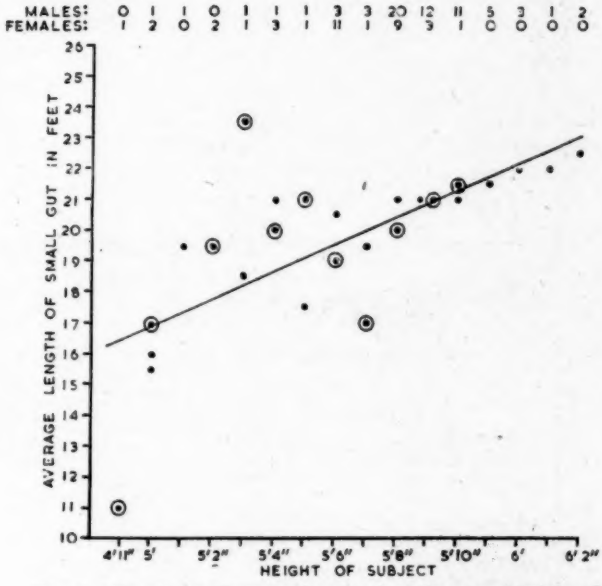

FIG. 4.—Correlation between length of small gut and height of subject. ●=Males; ⊙=females.

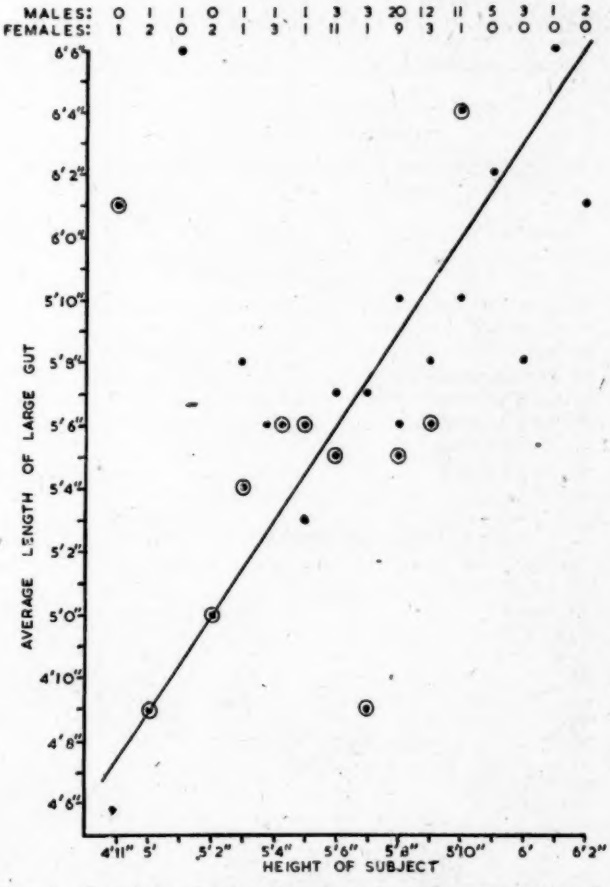

FIG. 5.—Correlation between length of large gut and height of subject. ●=Males; ⊙=females.

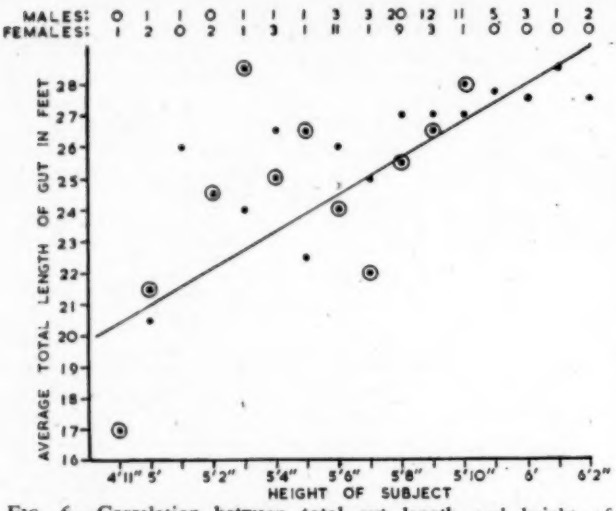
MALES: 0 1 1 0 1 1 1 3 3 20 12 11 5 3 1 2
FEMALES: 1 2 0 2 1 3 1 11 1 9 3 1 0 0 0 0
AVERAGE TOTAL LENGTH OF GUT IN FEET
HEIGHT OF SUBJECT
4'11" 5' 5'2" 5'4" 5'6" 5'8" 5'10" 6' 6'2"

FIG. 6.—Correlation between total gut length and height of subject. ●=Males; ⊙=females.

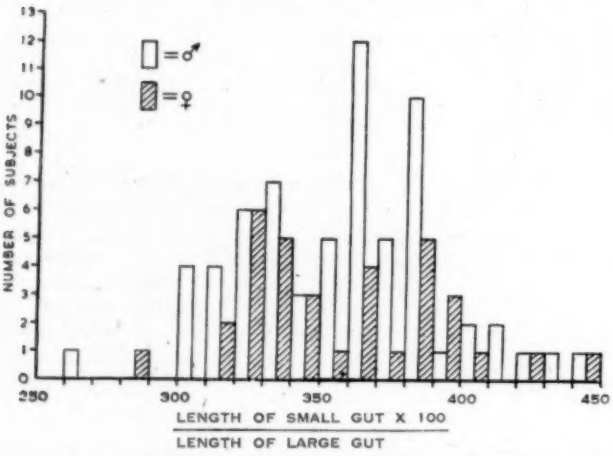

FIG. 7.—Correlation between length of small and of large gut.

the ileo-caecal valve. This patient lost a little weight post-operatively, but had no diarrhoea. Metabolic studies carried out one year after resection showed that albumin was deficient in her blood, but absorption and utilization of water, food, minerals, and vitamins were not seriously disturbed. Unfortunately this patient developed a recurrence of her growth, from which she died 18 months after the original resection. Still, it is comforting to the surgeon faced with an extensive resection to know that a patient can live an almost normal life with only a little over a foot of small intestine.

Effects of Small-gut Deficiency

It is usual, however, for patients having only a few feet of small intestine to develop fairly severe complications. The most trying of these is an intractable diarrhoea which cannot be stopped by any drugs but must be controlled by diet.

The chief absorptive defect is that of fats. These are well digested, but 45% of all ingested fat is excreted in the faeces, 80% of this being in the form of fatty acids (West *et al.*, 1939; Todd *et al.*, 1940). Calcium and vitamin D are lost with the fats and tetany readily develops. Carbohydrate utilization is normal, but 25% of dietary protein passes out in the faeces.

There is often "intestinal hurry" which leaves little time for the formation of vitamin B_{12} and K by bacterial action in the colon, so these vitamins must be supplied in the diet. In some patients a sprue-like hyperchromic megaloblastic anaemia develops, for which large doses of folic acid must be given.

Management

Lawrence (1953) outlined the treatment of patients subjected to a massive gut resection. In the immediate post-operative period, he stressed the necessity for blood transfusion and parenteral vitamins in addition to the usual gastric suction and intravenous fluid and electrolyte therapy.

As ileus passes off and the diet is increased, a watery diarrhoea usually begins. This is best controlled by frequent feeds of a non-residue diet containing abundant carbohydrates, a moderate amount of protein, and little fat. The patient should have adequate iron therapy, as this element is poorly absorbed after loss of the jejunum. He should take calcium, 1 g., and one polyvitamin capsule three times a day. His metabolic requirements should be kept low, so a quiet life is advised.

When these measures are adopted, the loss of a very large proportion of the bowel is not incompatible with health and comfort.

Summary

The small and large intestines of 65 male and 35 female subjects have been measured.

It is shown that there may be variations of as much as 100% in the length of the small intestine, but the large gut is much more constant in its dimensions.

Intestinal length in the adult is independent of age but is correlated with the height of the subject.

The deficiencies occurring after massive gut resection are described and a scheme of post-operative management is noted.

My thanks are due to Dr. J. T. Prendiville and his staff, notably Mr. P. Conlon, for their help and for permission to use the facilities of the department.

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The centenary of the birth of Sir D'Arcy Power (1855–1941) was commemorated by the Osler Club of London on November 11. Mr. W. R. LEFANU, librarian of the Royal College of Surgeons, spoke of D'Arcy Power's work as honorary librarian of the College. During his term of office at the College he greatly improved the library facilities. He encouraged younger men, especially in the study of medical history and biography, to which he himself made many contributions, including the revision and publication of Plarr's *Lives of the Fellows*. Dr. A. W. FRANKLIN paid a tribute to the character of D'Arcy Power, who had been a member of the Osler Club during its first ten years. The *Selected Writings of D'Arcy Power, 1877–1930*, presented to him on his 75th birthday, had been gathered together by the Club. It included a bibliography of 609 books and papers, including 184 biographies for the *Dictionary of National Biography*. Other speakers included Sir HARRY PLATT, P.R.C.S., and Sir D'Arcy Power's son, Air Vice-Marshal D'ARCY POWER. Dr. HAROLD AVERY presided.

THE ACCURACY OF MEASURING LEG-LENGTH DIFFERENCES

AN "OBSERVER ERROR" EXPERIMENT

BY

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The assessment of the differences in leg lengths is of importance in many aspects of medicine, and is a technique taught to all medical students. Because of appreciable differences between the recorded measurements of different observers it was decided to investigate the accuracy of this technique. The proportion of patients for whom all observers agree is a useful guide to the "observer error," but this criterion is somewhat limited—even if sufficiently reliable results for clinical purposes are being obtained—as "observer error" tends to increase with the accuracy of the measuring (e.g., the proportion of disagreements will be greater when measurement is to the nearest millimetre than when it is to the nearest inch). A statistical method is described for estimating the "observer error" in a more satisfactory manner.

Material and Method

The investigation was carried out at the Royal Air Force Medical Rehabilitation Unit, Collaton Cross. Of the 200 patients at the unit at the time, 50 were selected at random. The cases included in the investigation were: knee injuries (23), upper limb injuries (12), spinal injuries (8), leg injuries (5), effort syndrome (1), pes planus (1).

This group gives a reasonable selection of the conditions met at the unit, and might be expected to provide for the appearance of idiopathic and post-traumatic leg-length differences.

Leg lengths were measured by four doctors without reference to each other's results. They used the same metal-ended tape-measure. The patients were dressed in singlets and shorts, and were lying on an examination couch. Care was taken to ensure that the patient's heels were resting on the couch and that the knees were not flexed. The measurements were made from the anterior superior iliac spine to the tip of the medial malleolus. The tape-measure lay evenly along the inner border of the patella. Although the method is a standard one, there is no doubt that the conditions of the investigation led to a higher degree of accuracy than might be found in routine clinical practice. Differences in leg lengths were recorded to the nearest ¼ in. (6 mm.), the lower reading being taken in the case of intermediate values.

Results

Accepting ¼ in. (6 mm.) as the criterion for the diagnosis of "short leg," there was complete agreement in 20 (40%) of the 50 cases. When the criterion is changed from ¼ in. to ½ in. (12·5 mm.), the proportion of cases showing disagreement drops from 60% to 14%. In the cases that showed disagreement there was considerable variation in the number of doctors recording a short leg. When ¼ in. was accepted as the criterion, in many cases three or four doctors recorded "short leg," but their measurements differed from each other by ¼ in. or more. The results are summarized in Table I.

This method of describing the "observer error" is not entirely satisfactory, though it may be used as a general guide. In the first place, the estimate of error will increase if more accurate measuring is attempted. Secondly, it makes no distinction between systematic differences between observers and the variation which might result from repeated measurements by one observer on a single patient.

TABLE I

	Complete Agreement between All Observers		Disagreement between One or More Observers				Observer Error (Percentage Disagreement)
			No. of Observers Finding Short Leg				
	Leg Lengths Equal	Leg Lengths Unequal	1	2	3	4	
No. of cases: ¼ in. (6 mm.) criterion	17	3	11	8	7	4	60%
½ in. (12·5 mm.) criterion	40	3	4	3			14%

A Statistical Method of Measuring "Observer Error"

For the purpose of analysis, the difference in leg length to the nearest ¼ in., given by the length of the left leg minus the length of the right, is taken as the basic measurement. Thus short right legs yield positive differences and short left legs negative ones.

If the average of all four observers for each of the patients is taken, there is a good deal of variation between patients, as expected. Alternatively, by averaging over all patients for each observer mean values are obtained (Table II).

TABLE II.—*Mean Values for Recording Leg-length Differences*

Observer	Mean Values (in inches)	Mean Values (in mm.)
1	+0·065±0·017 ..	+1·65±0·43
2	+0·010±0·017 ..	+0·25±0·43
3	+0·045±0·017 ..	+1·14±0·43
4	+0·005±0·017 ..	+0·13±0·43
General mean ..	+0·036±0·009 ..	+0·91±0·23

Note.—The quantities following the ± signs are the standard errors of the means.

The standard errors have been derived from the analysis of variance given in Table III.

TABLE III.—*Analysis of Variance*

Source of Variation	Degrees of Freedom	Mean Square	Components of Variance
Between patients	49	0·1870	$v + 4v_P$
,, observers ..	3	0·0470+	$v + 50v_O$
Residual	147	0·0155	v
Total	199		

$F^+_{3,147} = 3{\cdot}0$. $P < 5\%$.

Table III may be used in another way. Each measurement is assumed to consist of the sum of four quantities, which can be calculated from the third and fourth columns: (*a*) an overall average value; (*b*) a term representing the true leg-length difference of a particular patient (variance $v_P = 0.0429$); (c) a term representing the systematic bias of the observer in measuring the difference (variance $v_O = 0.0006$); (*d*) a residual experimental error (variance $v = 0.0155$).

Discussion

Clinical observations may be very unreliable. Schilling *et al.* (1955) found observer errors ranging from 4 to 30% in the diagnosis of certain respiratory conditions. In measuring the blood pressure they found that two observers disagreed in 43% of patients by 10 mm. of mercury or more in reading the systolic blood pressure, and in 22% in reading the diastolic blood pressure. In measuring the chest expansion, a technique more comparable with the measuring of leg lengths, they found that two observers disagreed by ½ in. or more in 42% of cases.

The present investigation into the measurement of leg lengths also finds difference between four observers making estimates on 50 patients. Analysis of variance shows that

the difference between observer means is significant at the 5% level (Table III). This is rather surprising, as observed differences in leg lengths might be expected to be free from any systematic bias affecting a single measurement. The bias could depend on the order of the two measurements or on the handedness of the observers; but Observer 3 was left-handed and measured the left leg first, whereas the other three observers were right-handed and measured the right leg first.

The departures from the general mean are small, though significant, and are judged unimportant. The general mean (+0.036 in.—0.91 mm.), having a standard deviation of only ±0.009 in. (±0.23 mm.), is significantly greater than zero, but again is small. It is not possible from the data to say to what extent it is due to a real average difference in the patient's leg lengths or to a persistent bias in the observers.

The systematic differences between observers, though significant, are small, the main source of variation being an experimental error which would arise even with repeated determinations by one observer. What is much more important from the clinical standpoint is that the variations between observers are negligible compared with the residual variation, since the latter measures the variation to be expected if a single observer continued to make independent measurements on the same patient. This experimental error has a standard deviation of about $\frac{1}{8}$ in. (3 mm.), so that once in 20 times a single reading will be more than $\frac{1}{4}$ in. (6 mm.) out. Greater accuracy could be achieved by taking the average of several independent readings.

Conclusion

The overall degree of accuracy of the measurement of leg lengths is such that differences of $\frac{1}{2}$ in. (12.5 mm.) or more may be accepted as diagnostically significant, but differences of less than $\frac{1}{2}$ in. are not reliable unless based on the average of at least four measurements.

Thanks are due to Squadron Leader D. J. E. Cheshire, Flight Lieutenant C. E. A. Thomas, and Dr. C. P. Finch for measuring many legs. Permission to publish this paper was granted by the Director-General of Medical Services of the Royal Air Force.

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TREATMENT OF SEVERE SHOCK BY NORADRENALINE

REPORT OF FOUR CASES

BY

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L-Noradrenaline bitartrate ("levophed") is a powerful peripheral vasoconstrictor drug which produces a rise in both systolic and diastolic pressures (Swan, 1949). The clinical indications for its use include the treatment of hypotensive circulatory states due to a lowering of the peripheral resistance (Churchill-Davidson, 1951). In the following four cases the intravenous infusion of L-noradrenaline caused a dramatic sustained rise in blood pressure and appeared to be a major factor in the recovery from seemingly irreversible shock.

Case 1

A man aged 57 had a partial gastrectomy for duodenal ulcer performed by Mr. J. W. M. Sutherland in May, 1950. He was well until 4 a.m. on February 12, 1953, when he suddenly developed a severe haematemesis and was admitted to hospital. He was transfused with 7 pints (4 litres) of blood, and the blood pressure rose satisfactorily to 120/70. In the evening he collapsed again, and the blood pressure fell to 70/40. Surgical intervention seemed imperative, and at operation an hour later a stomal ulcer was found at the site of anastomosis and a second higher gastrectomy done. The operation lasted two and a half hours and 4 pints (2.3 litres) of blood was given intravenously. Forty minutes after operation the blood pressure was 60/40, and the patient was severely shocked. Methylamphetamine hydrochloride (15 mg. intravenously, 15 mg. intramuscularly) had no effect.

Half an hour later, in a last attempt to raise the blood pressure, intravenous noradrenaline was started, 4 ml. in 1,000 ml. of glucose–saline. At a rate of 20 drops a minute the blood pressure rose to 100/50 within a few minutes. The drip rate was increased to a maximum of 40 drops a minute within the next half-hour and the blood pressure rose steadily to 130/70. Thereafter ten-minute blood-pressure readings were taken and the drip rate was adjusted to keep the systolic pressure at 130. For an hour the rate varied between 20 and 30, and then gradual "weaning" from the drip was begun until it was finally stopped six hours after its commencement. Slow but steady improvement followed, but on the seventh post-operative day a phlebothrombosis developed in the right leg. Anticoagulants were given and the swelling subsided, but unfortunately on March 14 he developed sudden pain in the chest and died in two hours. Post-mortem examination revealed a large pulmonary embolus.

Comment.—Initial shock due to haemorrhage aggravated by operation.

Case 2

A man of 78 was admitted to hospital on October 26, 1954, with acute retention of urine. On examination he was fit and active for his age. The tongue was clean, and the heart and lungs were clinically normal. The blood pressure was 166/96. The bladder was distended to 2 in. (5 cm.) below the umbilicus. Rectal examination revealed an adenomatous enlargement of the prostate.

A self-retaining Foley catheter was inserted and the patient underwent a retropubic prostatectomy the following morning. The operation was without incident and lasted fifty minutes. Approximately 10 oz. (285 ml.) of blood was lost. The blood pressure at the conclusion was 140/80.

Two hours after operation bladder lavage was carried out and some clots were removed. The pulse rate was 86 and the blood pressure 136/78. Two hours later there was a marked deterioration. The patient was pale and sweating, pulse rate 120, blood pressure 80/60. A pint (570 ml.) of blood was given rapidly intravenously. Since there was no significant improvement a second pint was given intra-arterially. Preoccupied by the resuscitative measures, it was not noticed until after the intra-arterial transfusion that the bladder was distended and not draining. Manipulation of the catheter soon produced about 20 oz. (570 ml.) of heavily blood-stained fluid. Following the transfusions and release of tension in the bladder there was a moderate improvement. At 7 p.m. the blood pressure was 130/70 and the pulse rate 100. During the evening there was persistent blood-stained soakage from the wound followed by a further deterioration in the general condition.

A third pint of blood was started intravenously, and at 11 p.m. the wound was reopened under general anaesthesia. There was some venous oozing from the prostatic veins, which was controlled by a pack. At the end of the operation the blood pressure was only 60/40 and the patient seemed unlikely to survive. A noradrenaline drip, 4 ml. in 1,000 ml. of glucose–saline, was started. Within ten minutes, at a drip rate of 30 drops a minute, the blood pressure rose to 110/80 and was maintained at over 100 systolic by a drip rate varying between 20 and 25 a minute. Blood pressure readings were taken at 10-minute intervals throughout the night. At 10.30 a.m. the drip was stopped. Within five minutes the blood pressure fell to 70/40. Five minutes

after restarting the drip the blood pressure rose to 122/60. It was continued until the evening, when the rate was gradually slowed and the blood pressure was maintained. At 10.30 p.m. the drip was finally stopped without any concomitant fall in blood pressure, and thereafter the patient continued to improve. He was discharged home on the twenty-first day.

Comment.—Shock due to distension of bladder with blood aggravated by haemorrhage and second operation.

Case 3

A heavily built man of 43 was admitted to Victoria Hospital, Kirkcaldy, on October 19, 1954, with haematemesis and melaena. A barium meal in July, 1954, had shown a duodenal ulcer. Bleeding persisted over the next twenty-four hours, and he was transferred to the General Hospital for operation on October 20. Prior to operation he had received 5 pints (2.9 litres) of blood and 2 pints (1.1 litres) of "dextraven." His blood pressure on admission and before operation was 160/100, although it had fallen to 90/60 before transfusion was started. At operation no peptic ulcer was found. The liver and spleen were normal, but the entire alimentary tract contained a large quantity of blood. A high partial gastrectomy was performed. The operation was uneventful and lasted one and a half hours. When the patient was about to be taken to the ward he suddenly vomited and inhaled blood-stained stomach contents. He was immediately bronchoscoped and intubated. With pure oxygen he recovered, but his blood pressure, which at the end of operation was 160/100, dropped to below 60 systolic. The endotracheal tube was removed in half an hour, but within a few minutes he became cyanosed and then grey; respiration stopped and the pulse slowed to 10–15. Death seemed imminent.

Intubation, oxygen, and assisted respiration brought a dramatic improvement. First the pulse rate increased and the volume became stronger, followed by spontaneous respirations and loss of cyanosis. This sequence of events occurred on four further occasions, after the last of which the attacks did not recur. During these episodes 1 pint (570 ml.) of blood was given. The blood pressure, however, could not be raised above 70–80. Methylamphetamine hydrochloride, 15 mg. intravenously, had no significant effect. It seemed certain that the patient would soon die unless the blood pressure could be raised above 100 mm. Hg systolic. An intravenous infusion of noradrenaline, 4 ml. in 1,000 ml. of glucose–saline, was begun at 2 a.m., and the blood pressure quickly became stabilized at 140/90 with a drip rate of 18 drops a minute. Blood pressure readings were taken at five-minute intervals. At 5 a.m. the drip rate was slowed to 7 drops a minute, and at 6 a.m. the infusion was stopped and the blood pressure maintained. Despite the development of paralytic ileus and a partial disruption of the wound he made a complete recovery and was discharged on November 16.

Comment.—Shock due to inhalation of gastric contents and anoxia.

Case 4

A woman aged 20 was admitted to hospital on January 14, 1955, for observation as a case of possible ectopic pregnancy. On examination she was not shocked. The blood pressure was 130/80, pulse 76, and temperature normal. The diagnosis remained in doubt until the following day, when a vaginal examination revealed a soft mass in the right tube. At operation a tubal pregnancy was confirmed and the tube excised. About 10 oz. (285 ml.) of blood was removed from the peritoneal cavity.

On the second day she complained of upper abdominal pain and the pulse had risen from 80 to 110. On the third day the pulse rose to 120 and the temperature to 101° F. (38.3° C.), and in the afternoon she passed three loose green stools and vomited twice. At 8 p.m. her condition deteriorated further. She looked toxic and was sweating freely. The abdomen was moderately distended and only a few bowel sounds were heard. She passed three more green stools, which did not contain any blood or mucus. The blood pressure dropped to 80/40. Her conjunctivae were well coloured and there was no evidence of haemorrhage. A provisional diagnosis of peritonitis or a severe intestinal infection or necrosing enteritis was made. A pint (570 ml.) of blood was started at 11 p.m., by which time her blood pressure was unrecordable and her pulse was weak and irregular. The abdomen was more distended and bowel sounds were now absent. At 1.30 a.m. her extremities were cold and cyanosed. She was drowsy and apathetic. The blood and 250 ml. of normal saline had been given without any improvement.

A second drip with noradrenaline, 4 ml. in 1,000 ml. of glucose–saline, was started, and 1 g. of oxytetracycline was added to the first drip. Within fifteen minutes the blood pressure was 84/60 with a drip rate of 80 drops a minute. By increasing the rate to 100 a minute the blood pressure rose to 108/60 in an hour. Two hours later the dose of noradrenaline was doubled (8 ml. in 1,000 ml.), and the drip rate slowed to 60 a minute without any fall in pressure. This rate was maintained for three hours and then halved. The blood pressure did not fall. Further gradual reduction in the rate was possible, and the drip was finally stopped eleven hours after its commencement. The blood pressure was then 110/70. During the next three days she passed a total of 26 loose stools. No specific pathogenic organisms were cultured from these, but the clinical picture seemed to be that of a bowel infection rather than a peritonitis. Her temperature and pulse gradually subsided and she was discharged on the fifteenth day.

Comment.—Shock due to toxaemia.

Discussion

It is felt that noradrenaline should be used only when other "orthodox" methods have failed. In surgical practice the majority of cases of shock respond to adequate and prompt restoration of a deficient blood volume. Cases that respond in this way have already a normally functioning peripheral vasoconstrictor mechanism, and the additional constricting effect of noradrenaline is not required.

In Case 1 blood replacement that appeared to be adequate had no significant effect, although intra-arterial transfusion was not tried. It is obvious that the peripheral vasoconstrictor mechanism needed boosting. Similar cases have been described by Cappe and Pallin (1951), Churchill-Davidson (1951), and Shanahan (1955).

The primary collapse in Case 2 appeared to be due to distension of the bladder with blood. Some improvement followed intravenous and intra-arterial transfusions, but continued oozing from the prostatic veins and the administration of a second anaesthetic caused a profound peripheral circulatory failure, from which recovery seemed unlikely. As it was considered that the blood loss had been fully replaced no further transfusions were given. The administration of noradrenaline as a last resort resulted in an immediate elevation of the blood pressure and ultimate recovery.

In Case 3 the aspiration of gastric contents into the tracheo-bronchial tree, combined with anoxia in a patient who had undergone gastrectomy for haematemesis, caused a different mechanism of peripheral circulatory failure. The blood loss had been fully replaced and the most urgent initial treatment was to establish an adequate airway and to remove gastric contents from the trachea and bronchi. The repeated bronchoscopies and intubations lasted forty minutes. When this crisis was overcome and spontaneous breathing re-established the systolic blood pressure could not be raised above 80 mm. Hg. Ten minutes after starting noradrenaline the blood pressure rose to over 100 and was soon stabilized at 140/90.

These three cases illustrate common catastrophes in surgical practice. They responded almost immediately to

the noradrenaline. Their cold clammy extremities became warm and dry and the whole clinical picture of severe shock was altered dramatically. Nor did they require further blood at any time during their stay in hospital, which suggests that their blood loss had been reasonably replaced. The point that the beneficial effect of noradrenaline might have been obtained equally well by additional transfusions appeared highly unlikely at the time and there was an ever-present danger of overloading the already failing circulation.

In Case 4 the rising pulse and temperature, the diarrhoea, and the sudden onset of complete collapse without evident haemorrhage suggested an overwhelming toxaemia as the aetiological factor. Whether this resulted from peritonitis or bowel infection was at the time an academic question, and from past experience the administration of noradrenaline held out some hope of temporary recovery, while the simultaneous use of oxytetracycline was designed gradually to control the infection. The use of noradrenaline in severe toxic states has been described by Skelton *et al.* (1952) and Kurland and Malach (1952), with encouraging immediate results, although ultimate survival depended on the subsequent successful treatment of the underlying disease.

The use of noradrenaline requires constant supervision. Initially the blood pressure should be taken every minute and the drip rate varied according to the response. When the blood pressure is stabilized a reading every five to ten minutes should be sufficient. A concentration of 4 ml. in 1,000 ml. of glucose–saline was adequate in the first three cases. In the fourth case the concentration was doubled two hours after onset, since with a rate of 80 drops a minute signs of pulmonary oedema were beginning to develop. In cases of cardiac infarction where excessive infusion would overload the circulation, concentrations of 8 ml. and 16 ml. have been used (Smith and Guz, 1953).

Grayson and Johnston (1952) suggested that infusions of more than an hour or two may cause liver damage. In this small series the drug was given for six, twenty-three, four, and eleven hours without obvious ill effects.

Barlow *et al.* (1953) consider the results of noradrenaline so dramatic and reliable that in acute hypotensive states the use of other vasopressors has largely been discontinued. When the orthodox methods have failed it certainly seems justifiable to try the effect of noradrenaline.

Summary

The successful use of noradrenaline in four cases of severe peripheral circulatory failure is reported.

The cause of shock in two cases was haemorrhage and post-operative collapse; in one case post-anaesthetic aspiration of gastric contents combined with anoxia; and in the fourth case, toxaemia.

Three patients made a complete recovery. One patient died from pulmonary embolus thirty days later.

The use of noradrenaline is advocated as a last resort when the usual methods of resuscitation have failed.

The method of administration is described.

My thanks are due to Mr. J. W. M. Sutherland, who operated on Cases 1 and 4, for permission to publish them; to Dr. J. R. Kyles for his interest and help; and to the house-surgeons whose all-night vigils were so willingly undertaken and so amply rewarded.

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SKIN NECROSIS FOLLOWING INTRAVENOUS NORADRENALINE

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Intravenous L-noradrenaline, because of its general vasoconstrictor properties, is of great value in hypotensive states, but on occasion it may produce extreme local vasoconstriction that results in necrosis of tissues. This complication has occurred five times in three recent cases, in which the use of noradrenaline in an intravenous drip was followed by gangrene of the skin and subcutaneous tissues overlying and around the recipient vein. In each case the drug was administered in 5% dextrose or normal saline solutions through a metal cannula tied into a superficial vein. The patients had shown a marked degree of shock before the infusion was begun.

The case reports are given in some detail, as we believe that they indicate the pathogenesis of the complication and its means of prevention.

Case 1

A girl aged 18 was admitted to the Liverpool Royal Infirmary suffering from chronic ulcerative colitis. A subtotal colectomy with ileo-colic anastomosis was performed on January 18, 1955. Her post-operative condition was good until the early hours of January 21, when she was found to be in a state of extreme shock with a feeble pulse of 140 a minute and a systolic blood pressure of 40 mm. Hg. No cause for the collapsed condition was evident. Since the operation intravenous dextrose and saline with oxytetracycline had been given through a cannula tied into the left internal saphenous vein at the ankle. An infusion of 0.5 litre of 5% dextrose containing 2 mg. of noradrenaline was then begun through the same apparatus. The blood pressure rose to 80–90 mm. Hg, but after 150 ml. of the solution had been given in just under an hour it was noticed that the skin on the inner aspect of the left leg was mottled blue and white in colour, and very cold. The drip was stopped and the cannula removed.

As the peripheral veins were collapsed a similar cut-down drip with tied-in cannula was set up in the right internal saphenous vein at the ankle, using 2 mg. of noradrenaline in 0.5 litre of 5% dextrose. Marked pallor of the skin overlying the vein was noticed immediately, and one hour later there was a mottled discoloration similar to that in the left leg. The patient's general condition improved and the blood pressure was maintained at over 100 mm. Hg, but immediately the drip was slowed the pressure fell. Nine hours later the discoloration on the inner aspect of each leg had condensed to a uniform purple ellipse of skin about 4 in. (10 cm.) wide extending from 1 in. (2.5 cm.) above each skin incision almost to the knee. No further noradrenaline was given, and 5 ml. of 0.5% procaine and 50 mg. of papaverine sulphate were injected into the drip before it was stopped.

50 ml. of 0.5% procaine containing 2,000 units of hyalase and 80 mg. of papaverine sulphate were infiltrated subcutaneously around the affected part in each leg. Twenty-

four hours later the patient's general condition was good and the systolic blood pressure was 110 mm. Hg. The legs were painful and the areas of discoloration, which were insensitive to touch, had diminished in size and each was surrounded by a red raised zone of erythema. Further diminution in the extent of the involved skin took place, especially in the right leg, over the next week. On February 9 the necrotic tissue, consisting of skin and superficial fascia, was excised from each leg. On the right there were two areas of slough measuring 3½ by 1½ in. (9 by 3.8 cm.) and 1¾ by 1 in. (4.4 by 2.5 cm.), and on the left an area of 9 by 3 in. (22.8 by 7.6 cm.). Three weeks later skin grafting was successfully carried out, and on discharge on April 27 the legs were healed.

Only about 0.5 mg. of noradrenaline was given through the left internal saphenous vein, but the infusion had already been running for about 60 hours before the noradrenaline was begun. In the right leg a total of 10 mg. of noradrenaline in 2 litres of fluid was given over a period of ten hours. The maximum concentration used was 8 mg. per litre of dextrose or saline solution.

Case 2

A married woman aged 63 was admitted to the David Lewis Northern Hospital, Liverpool, suffering from a carcinoma of the posterior vaginal wall infiltrating the rectum. At operation on February 1, 1955, panhysterectomy and synchronous combined abdomino-perineal resection of the rectum with the posterior vaginal wall were performed. Just before the conclusion of the operation the patient's blood pressure fell to an unrecordable level and the pulse rate rose to 130 a minute. Two pints (1,140 ml.) of blood had already been given through a needle inserted percutaneously into a vein of the right forearm. A further pint (570 ml.) of blood containing 10 mg. of noradrenaline was given through the same apparatus with improvement in the patient's general condition and a rise in blood pressure. After operation the infusion was continued with 5% dextrose containing noradrenaline in a concentration of 12 mg. per litre. After a total of 3 litres of fluid had been given in a period of 24 hours the needle slipped from the vein and there was a slight leak of the solution into the subcutaneous tissues of the forearm before the drip was stopped. No local complications resulted. There was an immediate fall in blood pressure, necessitating intravenous noradrenaline being started, and being continued as follows:

February 2 and 3.—In 48 hours 6 litres of fluid containing 72 mg. of noradrenaline was given through a cannula tied into a vein on the dorsum of the right foot. The vein thrombosed and the infusion stopped spontaneously. No local complications developed.

February 4–8.—In five days 15 litres of fluid containing 180 mg. of noradrenaline was given through a needle inserted into a vein in the right forearm. The infusion stopped spontaneously because of venous thrombosis. There was local oedema but no other tissue reaction.

February 9.—In 24 hours 3 litres of fluid containing 36 mg. of noradrenaline was given through a needle in a vein in the right antecubital fossa. The vein thrombosed, but there were no other local complications.

On February 10 an infusion was started through a cannula tied into a vein at the left ankle. After 48 hours the skin over the vein on the inner aspect of the leg was cold and showed a blue-white discoloration. There was no swelling and the infusion was running freely when it was discontinued. The vein had received 6 litres of fluid containing 72 mg. of noradrenaline.

February 12 and 13.—In 48 hours through a needle in a left forearm vein 6 litres was administered containing 72 mg. of noradrenaline.

On February 14, for the first time since the operation, the patient's blood pressure was maintained at 100 mm. Hg without artificial aid. The inner aspect of the left leg showed a dark-blue area of necrotic skin measuring 8 by 1½ in. (20 by 3.8 cm.) overlying the recipient vein. The lower limit of discoloration was ¾ in. (1.9 cm.) above the skin incision.

Ten days after operation a vesico-perineal fistula developed and on February 23 this was repaired through a suprapubic transvesical approach. On February 29 laparotomy was necessary for small-bowel obstruction and an enteroanastomosis to short-circuit obstructing adhesions was performed. During this operation the patient's blood pressure fell to an imperceptible level and a noradrenaline infusion through a tied-in cannula was begun in a vein on the radial aspect of the right wrist. The concentration of the drug was initially 4 µg. per ml., but this was later increased to 8 µg. per ml. After 26 hours, when a total of 8 mg. of noradrenaline had been given in 1.5 litres, the radial aspect of the forearm became oedematous and the skin showed a discoloration identical with that in the leg. The drip was running freely until it was discontinued. Twenty-four hours later there was an area of necrotic skin measuring 6 by 1¾ in. (15 by 4.4 cm.) over the course of the recipient vein on the forearm. The lower limit was 1 in. (2.5 cm.) from the skin incision (Fig. 1).

FIG. 1 FIG. 2

FIG. 1.—The forearm in Case 2, showing the extent of skin necrosis and its relation to the incision. FIG. 2.—The leg in Case 2 during the stage of separation of sloughs.

The areas of necrosis on the forearm and leg were treated with eusol applications and the sloughs gradually separated, leaving granulating surfaces (Fig. 2).

Case 3

A man aged 49 was admitted to the Liverpool Royal Infirmary complaining of dysuria. A difficult urethral dilatation for stricture was performed under general anaesthesia on March 10, 1955. Six hours later he had a rigor and was unable to pass urine. Eighteen hours after the operation he was found to be in a state of collapse with rapid, feeble pulse and a systolic blood pressure of 65 mm. Hg. Only a few drops of blood-stained urine had been passed. As the limb veins were collapsed a drip infusion of noradrenaline in 5% dextrose solution was started through a cannula tied into the right internal saphenous vein at the ankle. There

was a satisfactory response and the blood pressure was maintained at about 120 mm. Hg. A moderately distended bladder was drained by suprapubic cystostomy, performed under local analgesia.

Forty-six hours after starting the infusion it was found that there was a strip of skin measuring 7 by 1½ in. (17.8 by 3.8 cm.) overlying the internal saphenous vein in the leg, which was purple in colour and was surrounded by a zone of erythema; the discoloration began 1 in. (2.5 cm.) above the incision. The drip was immediately stopped. The discoloured area of skin gradually decreased in size, and eighteen days later a slough of skin and subcutaneous tissue measuring 2½ by ¾ in. (6.4 by 1.9 cm.) was excised.

After further urethral dilatation the patient was able to pass urine normally. The leg was healed when he was discharged on April 29.

Initially, the concentration of noradrenaline solution used was 4 μg. per ml., but later, because of oliguria and raised blood urea in spite of high fluid intake, the quantity of intravenous fluid was reduced and a concentration of 16 μg. per ml. was used to maintain the blood pressure. In all, 66 mg. of noradrenaline was given in 7 litres of fluid during a period of 46 hours.

Discussion

We believe that the necrosis of tissue is due to intense prolonged arteriolar vasoconstriction produced by a high local concentration of noradrenaline. Deterling and Apgar (1951) recorded a case of skin sloughing following paravenous leakage of the solution. Greenwald *et al.* (1952) described two cases in which skin necrosis in the leg occurred in shocked patients; they thought that there was direct extravasation of noradrenaline into the subcutaneous tissues, probably due to the needle or cannula slipping from the vein. In Bergmann's (1953) three cases, however, a cannula or "polythene" catheter had been tied into the vein, and he thought that the hydrostatic pressure of the entering fluid was higher than the venous pressure and that noradrenaline solution passed along the tributaries of the vein and thence to the capillary and arteriolar bed, causing vasoconstriction and ischaemia. In our cases a tied-in-cannula had been used on each occasion when the complication subsequently occurred. The strict localization of the necrosis to the skin and subcutaneous tissues overlying and around the recipient vein, combined with the fact that its distal limit corresponded with the position of the tip of the cannula, suggests that the solution diffused through the vein, possibly owing to ischaemia of its wall caused by constriction of the vasa vasorum. There was no venous thrombosis, because in each instance the infusion was running well when skin discoloration was noticed. The skin incisions used for insertion of the cannulae healed by first intention.

Bergmann (1953) was of the opinion that the duration of the noradrenaline infusion was important, and found that, of eight recorded cases of skin gangrene, seven did not occur until the second day. In Case 1 of our series the complication occurred in both legs. The infusion in the right lasted for ten hours; in the left the vein lining had probably been damaged by the previous infusion, for sixty hours, of dextrose and saline solutions containing oxytetracycline. Noradrenaline was infused for only one hour. It is evident, therefore, that skin necrosis may follow a short period of intravenous noradrenaline therapy.

We believe that the two important factors resulting in tissue necrosis are shock and a high concentration of noradrenaline in the recipient vein. The latter is related more to the technique of administration than to the concentration of the drug in solution.

In our three cases, and in all other recorded cases of this complication of noradrenaline therapy, a common factor has been the presence of severe protracted arterial hypotension. The resulting hypoxia of the skin and subcutaneous tissue in the limbs renders them unable to withstand the further reduction in oxygen tension produced by the local vasoconstriction.

With regard to the second factor, in Case 1 the maximum concentration of noradrenaline solution infused by cannula in the left leg was only 4 μg. per ml. We have had experience of one case of prolonged hypotension and anuria in which a concentration of 32 μg. per ml. was used without local complications. With this patient the drug was given through a needle placed in an antecubital vein percutaneously. A similar technique has been used in many cases of prostatectomy performed under spinal analgesia without ill effect, although transient blanching of the skin overlying the vein has on occasion been noted. Case 2 received noradrenaline infusions of equal concentrations into seven superficial veins. Skin necrosis occurred over two of the three veins in which a tied-in cannula was used. With the four percutaneous infusions there were no local complications. This evidence indicates that the concentration of the drug in the solution as administered is not significant, but that the actual concentration in the vein lumen is extremely important. When the noradrenaline is given through a needle inserted percutaneously into a large vein it is rapidly diluted by the circulating blood, whilst if a tied-in cannula is used the recipient vein contains noradrenaline solution only and is thus exposed to a high concentration of the drug until it is joined by a large tributary.

When noradrenaline is to be given to a shocked patient we suggest that the complication of skin gangrene may be prevented by administering the solution either through a needle into a large superficial vein or, if the veins are collapsed and a cut-down is necessary, through a polythene tube passed far enough proximally to enable its tip to lie in a vein of considerably greater diameter than its own. Both these methods allow rapid dilution of the drug by the venous blood stream. If the skin overlying a vein receiving noradrenaline shows colour changes other than slight blanching the infusion should be stopped immediately. The early injection of procaine and papaverine into the vein may possibly relieve the local vasoconstriction and prevent tissue necrosis or reduce its extent.

Summary and Conclusions

Five instances of skin necrosis following intravenous noradrenaline are recorded in three patients. The pathogenesis of the lesions is discussed, and it is concluded that the main factors in its development are arterial hypotension and infusion through a tied-in cannula. It is suggested that the complication may be avoided by using a technique which permits rapid dilution of the drug by the circulating blood.

We are grateful to Professor Charles Wells, Mr. J. B. Oldham, and Mr. J. Howell Hughes for permission to record these cases and for their interest and advice in the preparation of this report. The skin grafting in Case 1 was performed by Mr. R. P. Osborne.

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The British Dietetic Association has issued a pamphlet on the functions and status of dietitians (Leaflet BDA/4), as it considers the position of dietitians in the hospital service needs clarification. "At the present time," it observes, "there is a shortage of qualified dietitians, insufficient to allow the proportion of even one to every hospital of 150 beds or more. The British Dietetic Association therefore urges that steps should be taken wherever dietitians are employed to ensure the utmost economy of staff and administration, so that dietitians are being used only for the very specialized work for which they have been trained, and are given adequate assistance by qualified cooks and by cleaners."

L-NORADRENALINE IN TREATMENT OF ACUTE COR PULMONALE

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Referring to cases of massive pulmonary embolism, Wood (1950) states: "The great majority . . . survive the initial insult; but about one-third die subsequently from circulatory obstruction. . . . On the other hand, about two-thirds recover—within hours, days, or weeks. Throughout this anxious period there is a 25% risk of another, and perhaps fatal, embolus."

While the immediate and intensive administration of anticoagulants is a valuable contribution towards the prophylaxis and treatment of the thrombo-embolic state, there is an equally urgent demand for measures to combat the profoundly hypotensive condition resulting from massive pulmonary embolism. The use of L-noradrenaline in the treatment of the shock and hypotensive state of acute myocardial infarction (Shirley Smith and Guz, 1953) would logically call for its application to cases similarly affected by acute cor pulmonale; but at the time of writing only one published case appears to have been reported (Wolff, 1954).

The following case report illustrates the extremely high concentration required in the delivery of L-noradrenaline (in the form of "levophed") over a prolonged period (during which two further episodes of pulmonary embolism took place) in order to sustain the blood pressure after a massive pulmonary embolism. A total of 798 ml. of levophed was required over a period of 11 days, yet profuse sweating was the only possibly toxic effect observed.

Case Report

A man aged 49 underwent partial gastrectomy for gastrointestinal haemorrhage from a duodenal ulcer on June 14, 1955. No cardiovascular abnormality was present preoperatively, and his blood pressure was 140/80.

At 6.30 p.m. on June 23, on getting up to go to the toilet, he collapsed, with sudden onset of marked sweating, pallor, and dyspnoea, but there was no chest pain. There was a tachycardia of 130, his blood pressure was about 80/40, but no engorgement of the cervical veins could be made out, and cardiac examination showed no abnormality apart from the tachycardia. An electrocardiogram (E.C.G.) was immediately carried out, and showed the typical changes of acute cor pulmonale. In standard leads I and II there was a deep S wave with "staircase" ascent of the S–T interval, and a Q wave in standard lead III (McGinn and White, 1935). Unipolar limb leads showed a very prominent R wave in aVR, an S wave in aVL, and absence of a Q wave in aVF (Phillips and Levine, 1950). Unipolar chest leads showed shift of the transition zone to V_6, with rather flat T waves in V_1 and V_2. On repeating the E.C.G. four days later, there was deep inversion of the T waves in V_1, V_2, and V_3 (Wood, 1941). As he had a small haemoptysis next day, a portable chest *x*-ray film was taken; this showed slight loss of translucency at the left base, which became more pronounced on subsequent *x*-ray examinations on June 30 and July 6.

In view of the well-known predisposition to pulmonary embolism after partial gastrectomy (Barnes, 1937) combined with the clinical picture and confirmatory E.C.G. findings, massive pulmonary embolism was confidently diagnosed (in spite of the absence of any obvious source).

The patient was immediately given aminophylline, 0.48 g., and heparin, 5,000 units, intravenously, and pethidine, 100 mg., and heparin, 15,000 units, intramuscularly (the last repeated 12-hourly thereafter) and a course of ethyl biscoumacetate ("tromexan") was started with 600 mg., and doses subsequently as determined according to the one-stage prothrombin time.

By 7.30 p.m. his general condition was very poor, his blood pressure was about 75/?, and it was decided to start an intravenous infusion of levophed in order to improve his circulatory state. An initial strength of 4 ml. of levophed (equal to 4 mg. L-noradrenaline) in a litre of N/5 saline was begun, at an average drip rate of 30 drops a minute. This rate was varied from 25 to 35 according to the blood pressure reading, which was taken half-hourly until stability was achieved, and hourly thereafter until the infusion was discontinued. With the drip counter used, 30 drops corresponded to 1.4 ml. of the solution.

After an hour there was no improvement in his blood pressure, and a further 4 ml. of levophed was added, and thereafter further increments of 4 ml. every half-hour until 11.30 p.m. By this time the infusion strength was about 45 μg. of L-noradrenaline a minute. After a temporary rise the next day to 140, the systolic blood pressure again fell to 80, and therefore 64 ml. of levophed was added to each litre of infusion for the following four days (see Chart). This gave an approximate delivery of 90 μg. of L-noradrenaline a minute at a drip rate of 30 drops a minute. The day after the embolism his general condition appeared about the same, and an apical gallop rhythm had developed. Profuse sweating was still present, and continued to be striking until the end of the infusion, probably being partly attributable to the high concentration of the L-noradrenaline infusion (cf. in phaeochromocytomata).

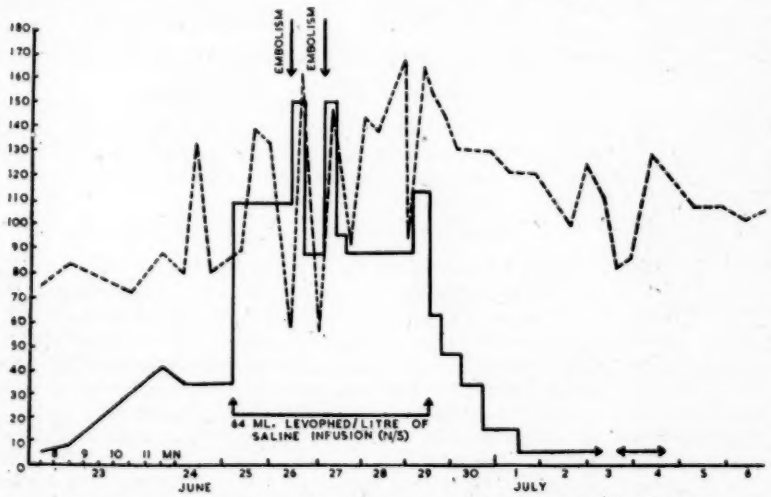

Chart showing the systolic blood-pressure readings and the dosage of L-noradrenaline. The dotted line represents the systolic B.P. (mm. Hg); the continuous line shows μg. of L-noradrenaline per minute.

The following day (June 25) his blood pressure and general condition had improved, but at 2.30 p.m. on June 26 he suddenly collapsed, with a very weak and irregular pulse, respirations at 32 a minute, and a blood pressure of 60/?. By 10.30 p.m., however, his blood pressure had improved to 165/90 as a result of increasing the drip rate to about 50 a minute, giving an infusion concentration of 150 μg. a minute, and the drip rate was accordingly slowed down again. On June 27, at 2 a.m., he again collapsed with severe precordial pain and a blood pressure of 65/35, but by 9.30 a.m. increase of the drip again to 50 a minute resulted in improvement to 150/75.

Although an E.C.G. taken on June 27 showed no evidence of rotation in the standard or unipolar limb leads (except for a persistent Q_3) and the transition zone in the chest leads had moved back to V_4, it was assumed that further embolism had occurred. Intravenous heparin, 10,000 units, was given six-hourly instead of by the intramuscular route, and no further embolic episodes were observed.

On June 29 his blood pressure appeared to be stabilizing at about 160/80, and the strength of the infusion was gradually diminished, until it was stopped on July 3. A temporary fall in blood pressure to 85/50 necessitated restarting for about 24 hours, after which the infusion was permanently discontinued, and his blood pressure gradually became established at about 110/60.

The course of his illness was additionally complicated by moderately severe haemorrhage from the gastro-intestinal and urinary tracts (after the infusion had been stopped), due to temporary difficulties in adjusting his anticoagulant treatment, and by severe thrombophlebitis of the successive veins used for his infusion. Recovery from the acute cardiopathy was considered to have been reached by July 23, and he was discharged home on August 4.

Comment

Pulmonary embolism continues to remain the most sinister and justly dreaded of post-operative complications. It still robs surgeons of the fruits of careful and technically excellent operations, and it is a deadly interloper in many other spheres of medicine.

Apart from the supremely important problem of prophylaxis, any contribution to the treatment of a condition with a fatality rate of *at least* 33% is to be welcomed. The use of L-noradrenaline appears to be just such a contribution, and deserves to be widely appreciated. Although many readers are doubtless well aware of its value, the extreme paucity of references in the literature to its use in acute cor pulmonale would seem to justify presentation of a further case so treated.

There would appear to be a definite place for the use of L-noradrenaline in domiciliary practice. Hunter (1955) comments: "Those who have suffered a massive (pulmonary) embolism with shock and circulatory collapse are not fit to move. . . . Difficult though the treatment may be to carry out in the home, therapy . . . should be carried out there until the patient is sufficiently recovered to withstand the stress of the journey." In such cases, resuscitation with L-noradrenaline could be started in the home, until the blood pressure appeared sufficiently stabilized for the patient to be fit for transfer to hospital. The drip could be kept running in the ambulance, and transferred with the patient to the hospital bed. A service on the lines of the obstetric "flying squad" would be required, since Euler (1955) has recently pointed out that, if hypotension is prolonged, vascular responsiveness to noradrenaline is eventually lost, and so the time-factor in instituting treatment is extremely important.

The danger of circulatory overloading by intravenous drip therapy, which is fully recognized in the presence of acute myocardial infarction (Shirley Smith and Guz, 1953), exists *a fortiori* in acute cor pulmonale, where an already well-nigh intolerable burden is placed on the right ventricle, without additional iatrogenic strain. For this reason the maintenance of an effective L-noradrenaline concentration with minimal drip rates is of paramount importance in pulmonary embolism. A delivery rate of a litre of infusion fluid in 12 hours appears to be safe from this point of view.

For short periods, in order to deal with special emergencies producing superimposed hypotension (recurrent embolism, as in this case, or even haemorrhage inadvertently produced through anticoagulant therapy), the concentration may need to be increased by temporarily speeding up the drip rate, when a maximum concentration of the infusion itself is already in use. In this case a concentration of 150 µg. of L-noradrenaline a minute was required on two occasions over a period of about eight hours, by increasing the drip rate to 2.5 ml. a minute, with an infusion strength of 64 ml. of levophed per litre in use. No circulatory overloading appeared to occur during these short periods, nor any evidence of toxicity, although the manufacturers of levophed do not appear to recommend a maximum strength exceeding one-seventh of the above.

In reporting the only previous case of acute cor pulmonale treated with L-noradrenaline, Wolff (1954) refers to an infusion of 16–20 µg. a minute for ten hours as "large doses." When the rate was increased to 24 µg. a minute toxic symptoms at once appeared. In the case herewith described, the patient had been receiving an infusion concentration of 110 µg. a minute for 30 hours, when recurrent embolism called for greatly increased concentration. Possibly by that time some degree of tolerance to the drug had been established, allowing for increase to 150 µg. without toxic effects.

Summary

In spite of the fact that massive pulmonary embolism, with its attendant state of hypotensive shock, is a common and often fatal emergency, only one reported case of the use of L-noradrenaline in treatment appears to have been published at the time of writing. A second case is reported, illustrating the value of this drug in treatment of the established state and two recurrences, in which a maximum concentration of 150 µg. of L-noradrenaline a minute was required over two periods of eight hours, and in which a total of 798 ml. of levophed was given in eleven days. Profuse sweating was the only evidence of any toxic effect, and recovery ensued. Wide recognition of this form of treatment is urged, including its use in domiciliary practice.

ADDENDUM.—Since this paper was submitted for publication Sibthorpe (1955) has mentioned the use of noradrenaline in a case of antenatal pulmonary embolism.

I would like to acknowledge the unremitting care and tireless attention in supervision of the infusion that was exercised by my house-physicians, Dr. B. Gupta and Dr. M. D. Enoch, and without which the patient's survival would have been most unlikely.

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Medical Memoranda

A Case of Vestigial Gall-Bladder

Apparent absence of the gall-bladder is such a rarity as to warrant its being recorded. In the present case a small nodule in relation to the common bile duct proved to be a vestigial gall-bladder.

CASE REPORT

A retired man of 79 was admitted to hospital on July 25, 1953. He had been well until eight weeks before admission, when he had begun to vomit an hour after his meals. In addition he had continuous nausea and a vague aching epigastric pain. At the same time he had noticed that his stools were pale and that his urine was dark. This was followed by jaundice which progressively increased. These symptoms persisted, and resulted in a considerable loss of weight. One month before admission he noticed generalized pruritus. There was no history of past attacks of jaundice or colic.

Examination showed him to be a thin elderly man, obviously jaundiced, but alert and cheerful. His tongue

was furred, the heart and lungs were normal, and the blood pressure was 150/80. There was no lymphadenopathy. The abdomen was slightly distended, and the liver tender and enlarged three fingerbreadths below the right costal margin. Rectal examination was normal, but the stools were clay-coloured. The urine contained a large quantity of bile. The haemoglobin was 13.9 g.% ; white blood count, 9,500, with a normal differential count ; blood group, O Rh positive ; serum bilirubin, 2.9 mg. per 100 ml. ; serum alkaline phosphatase, 30 K–A units ; thymol turbidity, 1 unit ; zinc sulphate turbidity, 6 units ; blood urea, 38 mg. per 100 ml. The pre-operative diagnosis was in favour of an obstructing neoplasm.

Operation.—An exploratory laparotomy was performed by Mr. J. B. Hume through a right paramedian incision on August 6. The liver was enlarged, but no gall-bladder could be seen. The common bile duct, when dissected, was found to be dilated into a tube 2 cm. across, and impacted within it was a single stone. On the right side of the duct at the porta hepatis there was a small body 1 cm. in diameter, which was removed for section. There was no connexion between this mass and the bile duct. The common duct was explored, but no further stones were found ; a T-tube was left in the duct.

The patient's post-operative course was uneventful. The jaundice rapidly faded, and the stools and urine returned to normal. Ten days after operation a cholangiogram showed a normal biliary tract, but no trace of a cystic duct or an intrahepatic gall-bladder. When last seen (October 29, 1953) he was well.

Histology.—Section of the mass removed showed it to be a small nodule with a hollowed centre ; there was a fibromuscular coat and a mucous membrane having the histological characteristics of gall-bladder mucosa. There was excessive underlying fibrosis.

Comment

Anomalies of the biliary tract are common, occurring in about 10% of necropsies, but absence of the gall-bladder is exceedingly rare. Latimer, Mendez, and Hage (1947) collected only 71 cases from the literature ; to these they were able to add three of their own. According to Gross (1936) the probable cause is a failure of the caudal portion of the embryological hepatic diverticulum to become tubular.

In our case the bud had become completely separated from its parent stem. In the previously reported 31 cases found at operation, 11, like ours, had an enlarged and dilated common bile duct containing stones. The discovery of this rarity was a welcome finding, and reversed a gloomy prognosis.

We are grateful to Mr. J. B. Hume for permission to publish this case, and to the Pathology Department of St. Bartholomew's Hospital for the histological report.

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Provocative Emetine in Diagnosis of Amoebiasis

It has often been suggested that examination of the stools after a " provocative " dose of emetine may yield a positive result in patients whose stools have previously been negative for *Entamoeba histolytica*. Hill (1946) recommended this method and stated that it was used in the Services as a routine in suspect but unproved cases. He regarded the effect of emetine in small doses as " provocative or stimulatory to the trophozoite." In 1947 he again stressed this, while evaluating various methods of diagnosis for intestinal amoebiasis. Brown (1946) was even more emphatic ; he practised this method for eighteen years and found it to " have rarely failed." He stated that when conditions become unfavourable for amoebae (due to emetine) cysts are passed out to seek a more accommodating host. Uninucleate and binucleate cysts were seen by him, the reason for this, he believed, being that the parasites were " finding a new host in a hurry."

However, Lawrence (1946) and Wenyon (1947) thought this method to be irrational and based on a mistaken analogy with the provocative dose of neoarsphenamine in serological diagnosis of syphilis. Dobell and Laidlaw (1926) reported that, in liquid medium, 1 in 5,000,000 of emetine hydrochloride was lethal to *E. histolytica*. The mode of amoebicidal action of emetine hydrochloride is not well known. However, there is nothing on record to show that emetine in small amounts is stimulatory to the parasite *in vitro*.

The data for or against the use of " provocative " emetine in the diagnosis of amoebiasis cannot be regarded as satisfactory. The object of the present study is to place on record our observation on the value of this method.

Material and Technique

Two groups were studied. We selected 18 patients who had shown signs and symptoms suggestive of intestinal amoebiasis, but in whom a single stool examination was negative. Three of them had been positive for *E. histolytica* in the past, but the symptoms had relapsed after varying periods of treatment, and two had an enlarged and tender liver. They were given 3 gr. (0.2 g.) of emetine bismuth iodide, and the next day, after a saline purgative—1 oz. (28 ml.) of saturated solution of sodium sulphate—as recommended by Hill (1946), the stools were examined. A similar test was carried out on 18 positive cases of amoebiasis passing cysts or trophozoites, or both, of *E. histolytica*.

In the first group, only one case was rendered positive for *E. histolytica*. Both cysts and trophozoites were found (Table I). The other 17 cases were negative. The test was repeated in the positive case, and after a second dose of emetine the stool was found to be negative.

In the second group only five remained positive for *E. histolytica* after " provocative " emetine (Table II). In the other 13 cases the stools were rendered negative. Even in the five cases which were still positive, the number of parasites was considerably reduced, and they appeared to have degenerated.

Table I.—*Provocative Emetine in* 18 *Suspected Cases of Amoebiasis*

Positive after provocative dose of emetine	1
Negative ,, ,, ,, ,, ,, ...	17

Table II.—*Provocative Emetine in* 18 *Positive Cases of Amoebiasis*

Positive after provocative dose of emetine	5
Negative ,, ,, ,, ,, ,, ...	13

Discussion

The above study shows that small doses of emetine have no stimulatory effect on *E. histolytica*. On the other hand, they have apparently rendered scanty infection still more scanty and diagnosis more difficult. This is amply borne out in the second group, where " provocative " emetine made the stools amoebae-free in 13 cases and in the remaining 5 the number of amoebae was considerably reduced and they appeared to be degenerating. In one case in the first group, however, *E. histolytica* was found after giving a dose of " provocative " emetine. This may be attributed to the effect of the purgative administered the next day. This method of administering " provocative " emetine cannot be recommended for diagnosis of suspected cases of amoebiasis in which ordinary smear examination is negative.

Our thanks are due to Sri B. M. Chakravarty for his assistance in this work.

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Reviews

ANATOMY AND PHYSIOLOGY OF THE LUNGS

Segmental Anatomy of the Lungs: A Study of the Patterns of the Segmental Bronchi and Related Pulmonary Vessels. By Edward A. Boyden, Ph.D. (Pp. 276+xviii; illustrated. £5 12s. 6d.) New York, Toronto, London: McGraw-Hill Book Company Inc. 1955.

The Clinical Physiology of the Lungs. By Cecil K. Drinker, M.D., D.Sc. (Pp. 84+ix; illustrated. 40s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications 1954.

These two books have in common the facts that both are written by men who have behind them many years of intensive study of their subjects, and that both should be read by everyone interested in the study of thoracic disease. Here the similarity ends, for the two books are quite different in method and in purpose.

Professor Boyden's book recounts in detail the results of nine years of intensive study at the University of Minnesota of the anatomy of the bronchial and vascular systems of the lungs. It begins with a critical review of previous work on the subject which resolves many confusions. In order to present his own findings Professor Boyden has had to adopt a rather complex system of lettering and numbering for the branches of the bronchi and vessels, but this system is logical, and, once grasped, should not lead to undue delay in understanding his text. The comprehension of complex anatomical detail of necessity demands painstaking concentration from the reader. The illustrations are numerous and clear. In the main part of the book the distribution of the bronchi and the blood vessels within individual lobes and segments is considered in detail, the commoner variations being enumerated; this part will naturally be of greatest interest to the anatomist and to the surgeon. A most interesting, though short, account of the development of the lungs in relation to gross congenital anomalies clarifies a subject which concerns the physician also. One is left with a feeling of respectful admiration for the immense industry and care which must have gone to produce this, the most complete and authoritative account of its subject hitherto published.

Professor Drinker's book is valuable in a different way. It is as refreshing as it is nowadays unexpected to find a book on clinical physiology of the lungs which does not deal with the minutiae of lung volumes and their subdivisions, the ventilatory function of the lung, and intrapulmonary gas mixing. Professor Drinker left these problems untouched, important as they are. His book is based on a series of lectures, given in the spring of 1950, in which he discussed the mechanisms by which the structural components of the lungs adapt themselves to different external and internal environments. It is full of stimulating suggestions, showing clearly what is known about these important adaptive mechanisms and in what respects our knowledge about them is incomplete. It can be read with profit by those interested in the physiology of the lungs at all levels: by the student for the example of clear physiological thought which he will obtain from it, as well as for the basic facts presented; and by the more experienced both for the pleasure of admiring so clear a statement of existing knowledge and for the stimulus to be derived from Professor Drinker's opinions on problems at the boundaries of knowledge.

J. G. SCADDING.

CLINICAL GENETICS

L'Hérédité en Médecine: Caractères, Maladies, Corrélations. By A. Touraine. (Pp. 875; 7,200 fr.) Paris: Masson et Cie. 1955.

Dr. Touraine's book on inheritance in medicine represents the first text on clinical genetics to be published in French; as such it is welcome. Unlike most first attempts, this is an extensive treatise, encyclopaedic in scope. About one-fifth of the text is devoted to general considerations; these are dealt with in detail, the ground covered being very much the same as Tage Kemp's *Genetics and Disease*. There is a particularly useful section on biometrical aspects. The various hereditary disorders are classified into four groups, according to whether they are generalized disturbances or affections essentially of ectodermal, endodermal, or mesodermal origin—a workable classification even if it breaks down at times. The different affections are described on a relatively uniform plan: a brief account of the clinical aspects is followed by a summary of the genetics of the affection and paragraphs on correlations or associated lesions. The illustrations are almost entirely pedigrees, and the 531 pedigrees given are themselves a useful summary of genetic knowledge. Each section carries its own references—a procedure not devoid of the considerable disadvantage of repetition.

In a book of this type, with its encyclopaedic approach, it is easy to point to defects or to stress comprehensiveness; and the latter is well illustrated by the fact that Christmas disease, described in this *Journal* as recently as December, 1952, is recorded and discussed. Actually the book is remarkably comprehensive; there is little of significance that is not noted—an achievement that must command respect. There is, however, a lack of balance in the text; some common genetic affections are dealt with only cursorily, and the genetic discussions, especially on the more abstruse disorders, are sometimes incomplete. Moreover, one would have liked to have the literature in English—by no means negligible—more adequately used and acknowledged.

This book should do much to stimulate the dormant interest in clinical genetics in the Latin countries, and to English readers it should be particularly valuable as a guide to Continental literature.

ARNOLD SORSBY.

X-RAY DIAGNOSIS OF BONES AND JOINTS

Bone and Joint X-ray Diagnosis. By Max Ritvo, M.D. (Pp. 752; illustrated. £7 5s.) London: Henry Kimpton. 1955.

This book describes the criteria on the basis of which a radiologist may be able to establish a diagnosis when studying radiographs of the skeleton. The subject-matter does not include the technique of radiography at all, nor are indications given regarding the value of stereoscopic or other views in difficult or unusual cases. The material is largely from Boston City Hospital, and the author, a radiologist, is on the staff of Harvard Medical School.

Each chapter is very comprehensive. The reader will find a clinical description of the majority of conditions he is likely to see in his lifetime. Developmental and metabolic disturbances of bone are described in some detail. Chapters on infection, bone tumours, and joint diseases provide ample clinical information for the radiologist. There is an interesting section on bone changes due to chemical substances and physical agents—poisoning by bismuth, fluorine, and radium, for example—and those due to electric burns. Illustrations of each of these would have been interesting. The author has limited the material on traumatic conditions of bones and joints to little more than the chapter on bone tumours, and this includes congenital dislocation of the hip, such conditions as Schmorl's disease, and bone-grafting. Fatigue fractures are mentioned, but in the case of ribs and tibia less usual terminology is used. The last chapter, on "soft-tissue roentgenography," is very instructive and well illustrated.

A large number of rare conditions, such as infantile cortical hyperostosis and lipochondrodystrophy, are included. The clinical description is adequate, and the reader is provided with references for "additional reading." The book will prove more useful when the diagnosis is established than as a means to that end. The reproduction of the many radiographs is excellent and the majority attract attention.

ST. J. D. BUXTON.

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INTELLIGENCE AND FERTILITY

Six years ago the report of the Royal Commission on Population[1] drew attention to the fact that "within each social group the more intelligent and the better educated have on the average smaller families than the others," and urged the need for intensive investigation into the problems thus raised. Whether or not these differences in fertility tend to "lower the average level of the nation's intelligence" the Commission was unable to say; but it recognized that "there is here an issue of the first importance." A number of researches were accordingly set on foot; and the results of several of the more important have now been published.

Earlier investigators, like Galton, Pearson, and their followers, had already demonstrated the inheritance of intellectual characteristics in man, and attempts had been made, by means of psychological tests, to estimate the average intelligence of the different social classes. The average birth rate within each class is known; and, with such figures as a basis, theoretical calculations can be made for the average level of the population at any future date. Different computers arrived at different results; and more than one was led to utter the most gloomy prophecies about the impending decline of national intelligence. But, as now seems clear, these armchair deductions had little value in the absence of more direct evidence. In particular they were largely invalidated by over-simplified assumptions about the manner in which mental characteristics appear to be transmitted. Surveys subsequently carried out in London revealed that, over a period of twenty-five years, no marked decline in the average level had taken place, though it still remained possible that the number of defectives might be increasing and the number of highly intelligent pupils diminishing. More detailed evidence on the whole question, therefore, was urgently needed.[2]

In 1947, following a suggestion of the Population Investigation Committee, the Scottish Council for Research in Education planned a mental survey, to be repeated at intervals of fifteen years, which sought to cover a complete cross-section of the population at the age of 11. As yet only preliminary analyses of the results are available.[3] The negative association between the size of the family and the intelligence of the children is fully confirmed. But on comparing the test results with those of an earlier survey carried out in 1932 it was discovered that the average score for the age-group selected had actually risen by a fraction of an I.Q. point. However, since the former survey had been planned with a different problem in mind, and since neither the tests nor the conditions of the testing were altogether comparable, the investigators refrain from drawing any final conclusion, and rightly emphasize that a series of such surveys will be necessary before any definite trends can be convincingly demonstrated.

More recent investigators have pointed out that the widespread changes which have lately taken place in social and economic conditions are likely to produce considerable modifications both in the relative fertility and in the genetic composition of the various occupational classes and of the nation as a whole. With increasing ease of travel and the rapid disappearance of class barriers, the social and local inbreeding characteristic of previous centuries is giving way to cross-breeding between widely different social groups and widely separated areas; and such changes, as history reminds us, are apt to be followed by quite unpredictable alterations in the mental constitution of the population as a whole. Evidence recently collected in this country and in the United States indicates that family planning and birth restriction are much more influenced by changes in education, economic security, and class tradition than was formerly assumed.[4] In this country the 1% sample tables published by the General Register Office on the basis of data secured during the 1951 census[5] disclose appreciable alterations both in the birth rate of the population as a whole and in the differential birth rate within various social classes. Thus, in 1911, 21.9% of the married women had families of five or more children; in 1951 only 4.4%. In 1911 the average number of live-born children per married woman was 1.9 for the upper and middle classes and 3.4 for the unskilled; in 1951 the comparable figures were 1.4 and 2.2. Thus, while general fertility has continued to decline, the differences in fertility which so alarmed the earlier eugenists have also diminished.

In certain groups fertility seems actually to be increasing. During the last two or three decades the marriage bar formerly imposed on women taking up certain posts or appointments has been largely removed, and, partly as a result, there has been a marked tendency for women to marry earlier. Some of the consequences are already discernible in an inquiry into the fertility of women graduates.[6] At Newnham College, of those graduating before 1900,

[1] *Report of the Royal Commission on Population*, 1949, London.
[2] *Papers of the Royal Commission on Population*, 1950, **5**, 61. London.
[3] Scottish Council for Research in Education, *The Trend of Scottish Intelligence*, 1949, London. *Social Implications of the 1947 Scottish Mental Survey*, 1953, London.
[4] Whelpton, P. K., and Kiser, C. V., *Social and Psychological Factors Affecting Fertility*, 1954. New York. (Reprinted from Milbank Memorial Fund Quarterly.)
[5] General Register Office, *One Per Cent. Sample Tables*, Part II, 1952. London.
[6] Hubback, J., *Eugen. Rev.*, 1955, **47**, 107.
[7] Fraser Roberts, J. A., *Introduction to Medical Genetics*, 1940, London. 227f. Penrose, L. S., *The Biology of Mental Defect*, 1949, 113f. London.
[8] Burt, C., *Eugen. Rev.*, 1955, **47**, 90.

only 25% seem ultimately to have married; of those graduating in the 1930's 60% were married by 1950. And, according to replies gathered from over 1,000 married women who had received degrees at various universities between 1930 and 1952, the size of their families is actually larger than the average for the general population. Thus the mean number of children born after ten years of marriage to those who had married before the age of 35 was 2.50, whereas in the general population it is only 2.02.

Meanwhile there has been much controversy about the inheritability of what Galton termed "general ability" and about the validity of so-called intelligence tests, such as those on which the Scottish surveys were based. It is clear that the cautious definition of intelligence advocated by several recent critics—namely, that which is measured by intelligence tests—is quite inadequate for the purposes of mental genetics. Recent research has emphasized the need for distinguishing more carefully between the observable manifestations and the intrinsic causal factors, between what geneticists call the phenotype and the genotype. Only a few special forms of mental deficiency, most of them severe and nearly all of them rare, prove to be directly determined by single genes, and in such cases the parents may appear to be of perfectly normal ability. For the most part, therefore, what is loosely called intelligence seems, like other continuously varying traits—stature, for instance, or size of head—to be the complex product of numerous genes whose influence is small, cumulative, and indirect, and whose ultimate effects are modified by various postnatal or environmental conditions.[7] Some such multifactor hypothesis now seems strongly confirmed by recent analysis of the distribution of intelligence among members of the same family.[8] Consequently, if the terms heredity, variation, and selection are still to be used, it must be recognized that their implications have been considerably altered. The whole issue thus appears far more complex than the pioneers of eugenics were prone to assume; and far more intensive research is required on both the psychological and the social aspects of the problem before any safe conclusions can be reached. Plainly, in these days of progressive social medicine and improved economic conditions, the problems of human genetics have become not less important but more important than they were two or three generations ago.

PREVENTION OF INFLUENZA

At this time of the year thoughts turn to influenza and the ways and means of controlling this formidable cause of acute respiratory disease.[1] Few viruses have been the subject of such intense research in recent years as have those of influenza, and it is right that this should be so, as Sir Macfarlane Burnet has recently emphasized.[2] In the first place influenza is a major cause of human disease, varying from the inconvenience of a mild respiratory illness to a devastating epidemic disease infecting hundreds of millions of the world's population, as it did in the 1918–19 pandemic. Secondly, to the biologist influenza is something of a model virus, providing a ready means by which basic problems can be examined—such as the nature and multiplication of viruses and details of the relationship between virus and host—to obtain a better understanding of virus infections as a whole.

A few years after the viral aetiology of influenza was established in Britain in 1933[3] attempts were made to immunize human beings against the disease.[4] For a number of reasons the results were inconclusive, and it was not until ten years later, when the full advantage of the developing chick embryo in influenza research came to be appreciated, that successful immunization against influenza was achieved. In 1943 the Commission on Influenza in the United States clearly established the protective effect of vaccination on U.S. army personnel in an influenza A epidemic.[5,6] The formolized vaccine, prepared from the fertile egg, contained both viruses A and B. In the winter of 1945–6 T. Francis, J. E. Salk, and W. M. Brace reported slightly better results with a similar vaccine against virus B.[7] In Britain, where virus B was also epidemic, limited observations suggested some degree of protection at two vaccination centres.[8] This was encouraging. But in 1947 an essentially similar vaccine was universally ineffective, both in the United States[9] and in this country,[10] largely due to the appearance early in 1947 of a new strain of virus A (A-prime) which differed antigenically from the A strain in the vaccine.

One of the many problems posed by the 1947 outbreak was how to incorporate in any future vaccine virus strains representative of those likely to be encountered in an epidemic. As a poliomyelitis vaccine must include all three strains of poliomyelitis virus, so must an influenza vaccine include at least viruses A and B (virus C seems hardly necessary at present). The difference in the protective value of vaccines in 1943 and 1947 indicated that a wider range of virus A strains would be necessary, and for the last few years the problem of antigenic variation of virus A has been closely studied.[11,12] Significant differences have been detected, as among the A sub-strains isolated from influenza outbreaks in Britain in 1951,[11] but it is not yet clear to what extent and to what degree this variation will progress. In accordance with these changes the composition of vaccines will have to be altered from time to time. On the other hand, news from the virus laboratory at Ann Arbor, Michigan,

suggests that such changes may be limited. K. E. Jensen and T. Francis[13] have produced evidence that, while differences among strains could be detected, extensive cross-relationships existed. An examination of pooled human sera from subjects of different ages was also made in the same laboratory and has produced some interesting information on the distribution of antibody. In this study F. M. Davenport, A. V. Hennessy, and T. Francis[14] have shown that the incidence of antibody to a given A strain varies according to age and with the period of prevalence of that strain. Thus antibody to A-prime is found in young children, Type A (PR8) antibody in young adults, and, of unusual interest, antibody to swine influenza in the 30-year-olds. The last finding may have a bearing on the origin of the 1918–19 pandemic, which P. P. Laidlaw twenty years ago suggested was related to swine influenza virus.[15] The initial antibody response in early life appears to be limited, and as the years go by the range of antibody seems to broaden but with reinforcement of primary antibody, a phenomenon which Davenport describes as "the doctrine of original antigenic sin." This work gives considerable encouragement to the development of influenza vaccines.

Formolized vaccines produce on the whole a shorter immune response than a live vaccine, and the problem now is to produce a sustained immune response at a high level. This aspect has been recently considered by an M.R.C. Committee on Influenza, whose second Progress Report appears in the *Journal* this week (p. 1229). Following the work of J. E. Salk and A. M. Laurent[16] on the use of mineral-oil adjuvants in influenza vaccines, a trial was carried out in 1953 with three vaccines (two adjuvant and one saline) to determine the serological responses and clinical reactions. The findings were in general agreement with previous reports on this subject. Antibody responses with adjuvant vaccines were enhanced and sustained with one-tenth the amount of virus antigen in the saline vaccine. One of the adjuvant vaccines with a mouse-adapted strain was found to be a better antigen that the equivalent egg-adapted strain, confirming some earlier experimental findings on this subject.[17] A number of reactions to vaccine were encountered, but the rate was not excessive. There were more local reactions with the saline vaccine, but on the other hand a few persistent local reactions were seen with the adjuvant vaccines.

The next stage is to compare the protective effect of this type of vaccine, and arrangements have now been made to put this to a practical test this year. Investigations of this sort are well worth while and require close co-operation between clinicians and virus laboratories.[18 19] As Drs. J. C. McDonald and B. E. Andrews conclude in a paper appearing at p. 1232 of the *Journal*, both serological and clinical tests are needed to extract the fullest information from a trial of vaccine. While nobody would wish for an influenza epidemic, recent improvements in technique may help to solve some of the problems now to the fore if we have one.

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2 Burnet, Sir Macfarlane, *Endeavour*, 1955, **14**, 5.
3 Andrewes, C. H., Laidlaw, P. P., and Smith, W., *Lancet*, 1934, **2**, 859.
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7 —— Salk, J. E., and Brace, W. M., *J. Amer. med. Ass.*, 1946, **131**, 275.
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10 Mellanby, H., Andrewes, C. H., Dudgeon, J. A., and Mackay, D. G., *Lancet*, 1948, **1**, 978.
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12 Isaacs, A., *Brit. med. Bull.*, 1953, **9**, 208.
13 Jensen, K. E., and Francis, T., *J. exp. Med.*, 1953, **98**, 619.
14 Davenport, F. M., Hennessy, A. V., and Francis, T., ibid., 1953, **98**, 641.
15 Laidlaw, P. P., *Lancet*, 1935, **1**, 1118.
16 Salk, J. E., and Laurent, A. M., *J. exp. Med.*, 1952, **95**, 429.
17 Isaacs, A., and Sampaio, A. A. de C., *J. Path. Bact.*, 1953, **65**, 613.
18 *British Medical Journal*, 1953, **2**, 1173.
19 Ibid., 1953, **2**, 1178.

SEPTIC ABORTION

Childbed fever was once the scourge of midwifery, but in Britain to-day a death from puerperal sepsis is rare. This striking improvement is not due to chemotherapy alone. Better antenatal care, improved methods of prophylaxis, and increasingly high standards of obstetrical and nursing practice have all contributed, and it is partly because these conditions are less likely to have come into play in cases of abortion that mortality from post-abortum infections has not fallen equally. The paper by Drs. A. M. Ramsay, E. H. Brown, and Stella M. Manners at page 1239 of the *Journal* this week is therefore timely, and their review of the diagnostic and therapeutic problems of septic abortion as reflected in nearly one thousand cases seen over the past five years is instructive. They believe that the common criteria of uterine sepsis, clinical, bacteriological, and haematological, are not in themselves indisputable evidence of uterine infection, because they may all be present when only the retained products are infected and disappear after the evacuation of the uterus. In particular, notifiable pyrexia may accompany an abortion without demonstrable uterine sepsis, while extrauterine spread may be associated with only a low-grade fever, especially in *Clostridium welchii* infections. The pulse rate is a more sensitive guide to the presence and progress of infection. Nor can the diagnosis of infection be made on the bacteriological findings alone, except when haemolytic streptococci of Lancefield Group A are recovered. In cases of septic abortion bowel-derived organisms are most commonly found, but these are usually saprophytes and require favourable factors for conversion to pathogens—and this applies to *Cl. welchii* too.[1] Similarly the white-cell count is not invariably high. Altogether, therefore, the diagnosis must rest on the sum total of clinical and other evidence, and in some cases the final assessment of the extent of infection cannot be made until the illness has run its course.

1 Ramsay, A. M., *J. Obstet. Gynaec. Brit. Emp.*, 1949, **56**, 247.
2 Burnett, C. W. F., *British Medical Journal*, 1952, **1**, 886.
3 Collins, C. G., Nelson, E. W., Ray, C. T., Weinstein, B. B., and Collins, J. H., *Amer. J. Obstet. Gynec.*, 1949, **58**, 1155.

As to management, Dr. Ramsay and his colleagues follow the lines set out in this *Journal* by C. W. F. Burnett.[2] The first measures comprise a general and pelvic examination, and the taking of cervical swabs, a catheter specimen of urine, and blood for haemoglobin estimation, grouping, and cross-matching. In the presence of rigors or high pyrexia a blood culture is advisable. A five-day course of combined sulphonamide and penicillin is started, but may be varied later according to the clinical response, the organisms recovered from the swabs, and the sensitivity tests made on them. Blood transfusion may be an urgent necessity, but the immediate evacuation of the uterus is infrequently indicated. Nevertheless, if there is no response to therapy, the removal of an incomplete septic abortion should not be delayed beyond 36 hours, unless there is evidence that the infection is widespread. Dr. Ramsay concludes that modern therapy has largely eliminated infection as a direct cause of death, and that acute renal failure has now become the most dreaded complication of post-abortive sepsis. Fewer than one-tenth of his cases were marked by extrauterine infection, but in other countries cases of neglected septic abortion are more commonly encountered. If suppurative thrombophlebitis ensues, such radical measures as ligation of the inferior vena cava and ovarian veins may be advised.[3] Nor should the importance of such general measures as high protein intake, extra vitamins, and nursing in the fresh air be overlooked. Cases of septic abortion are therefore best admitted to hospital, although preliminary attention at home by an obstetric flying-squad may be life-saving. The hospitals for their part must set aside an adequate number of beds for abortion cases. Finally, the subject of abortion cannot be considered without regard to its ethical aspects, and it is advisable for the doctor not to divulge any information to a third party without the patient's consent.

TREATMENT OF TOXIC GOITRE

It is only a little over a hundred years since Dr. Robert Graves died. If we could be transported back through time and join him at a ward round in the Meath Hospital, Dublin, the treatment of the disease associated with his name would appear much easier than now, though the results would be less satisfactory. At least three different methods of treating toxic goitre are now available, and it is not surprising if at times the decision on which one to use is difficult. The three forms of treatment—surgery, anti-thyroid drugs, and radioactive iodine—may be used singly or in combination. In the opening pages of the *Journal* this week we publish an article by Professor E. J. Wayne and his co-workers reviewing their experience with radio-iodine, and it helps to put this, the newest therapeutic approach, in better perspective.

It was J. H. Means,[1] of Boston, who emphasized that it was usually possible to distinguish hyperthyroidism arising in a nodular goitre from the variety seen typically in the younger patient with a smooth, uniformly enlarged gland. Surgery is the best treatment for the patient with a toxic nodular gland, but this is the only form of the disease for which opinion is unanimous about treatment.

Prolonged treatment with thiouracil[2] gives a disappointing relapse rate after the drug is stopped; about two-thirds of the patients have a recurrence of their symptoms no matter how long the initial course of treatment. Possibly such therapy is best suited to the rare cases of Graves's disease seen in children.

It is now about twelve years since S. Hertz and A. Roberts[3] treated the first patients with radio-iodine. The early therapy was carried out with an isotope of short half-life—namely ^{130}I—and it was much later that ^{131}I with its convenient half-life of eight days came into general use. Professor Wayne and his colleagues now review the isotope treatment of 140 hyperthyroid patients. The results are good, for 84% were made euthyroid and only 12% showed evidence of hypothyroidism. Most of their patients required only one dose, and, though these writers attempted a careful assessment of the dosage needed, the amount given seems likely to depend more on empirical than theoretical criteria: 7,000 rads are usually necessary to control the disease, and a single tracer dose gives information on the proportion taken up by the thyroid. Autoradiographs show that the uptake of isotope by the gland is spotty,[4] and an interesting attempt to make it more uniform was described by R. Fraser and his colleagues.[5] They administered a preliminary course of thiouracil, and then, on stopping the drug and administering radio-iodine, they found the amount of isotope fixed by the gland was enhanced. With this technique the thyroid is prepared for isotope therapy rather as for surgical thyroidectomy. Moreover, a smaller dose of radio-iodine is required.

The bogy in the radio-iodine treatment of thyrotoxicosis is the possibility of inducing cancer. However, the evidence seems to point against this being a real danger. The type of irradiation which the gland receives is short and sharp, and now that patients have been treated for at least twelve years some of them might be expected to have developed cancer of the thyroid if the therapy was in fact carcinogenic. Most clinics still take a conservative view and do not treat patients with an expectation of life of twenty years or more, but it may well be safe to treat younger people. Certainly this therapy has notable advantages. Whenever the patient cannot be prepared satisfactorily for a surgical operation, when earlier operations have been followed by recurrence of the disease, when during previous treatment a recurrent nerve or the parathyroid glands have been damaged—in all of these cases isotope therapy is best. The patient is in hospital for only a few days or may be treated without admission, and there is no operative or anaesthetic risk. The radio-iodine treatment of hyperthyroidism has undoubtedly come to stay. Only time can show if it increases the incidence of malignant change in the gland, and all the evidence so far weighs strongly against this.

[1] Means, J. H., *The Thyroid and its Diseases*, 1948, Philadelphia.
[2] Goodwin, J. F., Steinberg, H., and Wilson, A., *British Medical Journal*, 1954, **1**, 422.
[3] Hertz, S., and Roberts, A., *J. Amer. med. Ass.*, 1946, **131**, 81.
[4] Taylor, S., *Proc. roy. Soc. Med.*, 1953, **46**, 242.
[5] *Brit. J. Radiol.*, 1954, **27**, 23.

CARCINOGENIC PROPERTIES OF CITY SMOKE

A study of the effects induced in mice by solvent extracts of atmospheric smoke is being carried out by G. R. Clemo and his colleagues at Newcastle-upon-Tyne.[1] Clemo in an earlier publication[2] has written:

"Newcastle is a clean city as cities go, it has some murder-emitting chimneys and thousands of buses there as elsewhere belch forth their black smoke, all of which could be prevented. As but one instance of what must be hundreds, along one ten-mile stretch of main road between Newcastle and Hexham there are no fewer than eight schools and hundreds of buses and lorries emit black smoke along this route all the day long. It is impossible to state the extent of the damage to health thus incurred and probably only revealed after the lapse of years and all of it preventable.

"The smoke which I have been examining comprises that commonly present in large centres of population and industry, but its composition will also be affected by the proximity of three chimney stacks to the filters, two serving heating installations and fired with small coal, and the third an incinerator for the disposal of surgical and other refuse from a large hospital."

The experiments of Clemo *et al.* are not the first to be designed as a direct test of the carcinogenic activity of the material with which town air is polluted. The benzpyrene present in soot is the most obvious carcinogen to be examined, and this was done by R. E. Waller.[3] He also studied two other carcinogens—namely, the arsenic and radioactive material present in the atmosphere of towns. He found that the amount of benzpyrene in London air was of the order of 5 μg. per 100 cubic m. Since the "standard man" breathes about 20 cubic m. of air per 24 hours, his intake in 12 hours would contain 0.5 μg. benzpyrene, which is approximately the minimal dose of benzpyrene required to induce sarcomas in the mouse. (The minimum doses of different carcinogens required for tumour induction in the mouse have been detailed in a recently published semi-popular book on cancer.[4]) Waller finds the mean annual concentration of benzpyrene per 100 cubic m. of air in different English towns to be:

London (County Hall) ..	4.6 μg. benzpyrene/100 cubic m.
Sheffield	4.2 " " " "
Leicester	2.9 " " " "
Burnley	2.7 " " " "
Hull	1.8 " " " "
Bristol	1.3 " " " "

In the winter the benzpyrene content increases (domestic coal smoke being the main source) and on foggy days it rises higher still. In Sheffield on three foggy days it has been as high as 32.8 μg./100 cubic m.

Clemo *et al.* tested the benzene extract of town smoke (from the filters of their ventilating plant) directly by painting it in 1% solution on the interscapular region of mice of different pure strains. The numbers of animals used in each test were small: some of the tests were done on two mice; the most was six mice per test; whereas some investigators would prefer 50 or 100 animals for each experiment. So far as the results go, they indicate that, first, some of the constituents of smoke can induce nodules in the lungs of the mice; secondly, some can produce papilloma and epithelioma of the skin; thirdly, some can do both. Clemo's studies well illustrate an important feature of research in this field—namely, that not only do different strains of mice show different degrees of sensitivity to the carcinogens in smoke but that the tissues themselves (lung and skin) vary widely in their susceptibility. For example, when one particular fraction of smoke was tested on $A/_{rf}$ mice, lung nodules developed but not skin tumours. Another fraction induced skin tumours in $C_{57}BL/G_{.}$ strain but not lung nodules; the same fraction tested on A/G_{rf} mice gave lung nodules as well as skin tumours. Another fraction resulted in the development of skin tumours in $C_{57}BL/How$ mice but no lung nodules. Clemo *et al.* also tested extracts of the fumes from diesel engines. With these, lung nodules were obtained in the mice but no skin tumours, even in the most susceptible strains used. P. Stocks and J. M. Campbell,[5] in a study of lung cancer and atmospheric pollution in the North Wales and Liverpool Hospital Region, have recently stated that "the concentration of smoke and of 3:4-benzpyrene, other polycyclic hydrocarbons, and sulphur dioxide in the air rises with increasing urbanization, the benzpyrene figure in Liverpool being 8 to 11 times as great as in the rural localities examined." They found that the death rates from cancer of the lung in Liverpool exceeded the rates in the surrounding country independently of the amount of tobacco smoked, and concluded that the data available "justify a working hypothesis that benzpyrene might be the agent responsible for the associations of lung cancer with both smoking and urban residence."

The conclusions, and indications for further work, deriving from these researches will be of great interest to investigators working on the present fashionable theme in cancer research—the carcinogenic activity of tobacco smoke. One of the chief difficulties here is to find some tissue which has a sensitivity approximating to that of the human lung. This problem is being tackled by Sir Ernest Kennaway, who is conducting experiments in which human foetal lung growing in tissue culture is the test material.[6]

REASSESSMENT OF "NORMAL" VALUES

There is so much to learn that most of us accept without question so-called "normal" values as statements of authority; but they are often based upon just as tenuous evidence as the foundations of many clinical diagnostic and therapeutic dicta which have failed to stand the test of careful investigation. In recording new measurements scientists nowadays usually take care to define the limits of normality rather than state a simple average value, and to give the sources of measuring error. Recently physicians and radiologists have questioned their own assessments of what is normal and abnormal. They find that wide variations in opinion can exist, and that these differences arise partly out of the experimental error of the

[1] Clemo, G. R., Miller, E. W., and Pybus, F. C., *Brit. J. Cancer*, 1955, **9**, 137.
[2] —— *Chem. and Industry*, 1953, No. 37, 957.
[3] Waller, R. E., *Brit. J. Cancer*, 1952, **6**, 8.
[4] I. Hieger, *One in Six: an Outline of the Cancer Problem*, 1955, London.
[5] Stocks, P., and Campbell, J. M., *British Medical Journal*, 1955, **2**, 923.
[6] Kennaway, E. L., *32nd Annual Report of the British Empire Cancer Campaign (covering 1954)*, p. 98.

[1] Alvarez, W. C., *Gastroenterology*, 1940, London.

measuring process, and partly because each measurer tends to impose a personally characteristic bias upon his measurements. These iconoclastic incursions are steadily being extended to concepts which carry the added authority of age. This is a salutary process and one to be encouraged. Many accepted normal values are based on not very good statistical material and are expressed in too rigid a form to be reasonable. Indeed, the older the value the more likely is it to need fresh thought and reassessment by modern statistical methods.

The papers in this issue of the *Journal* by Squadron Leader P. J. R. Nichols and Mr. N. T. J. Bailey and by Miss B. M. L. Underhill remind us of some of the factors which have to be considered in deciding what is normal and abnormal. Nichols and Bailey discuss the errors of measurement rather than the measurement itself. Advancing beyond the statement that normally both legs are the same length, they calculate how different the lengths must appear to be before being judged as abnormal. Underhill discusses the measurement itself. What is the "normal" value, how should it be expressed, and what is its meaning? Authority states that the normal average length of the small intestine is 22 ft. (6.7 m.) but says nothing about what is abnormal. Intestines that have functioned well in life apparently may be anything from 11 to 25 ft. (3.3 m. to 7.6 m.) long post mortem. The real range of normality may be even greater, and, to complicate the picture further, the length of gut must be judged in relation to body length. During life, however, the small intestine is less than half this length[1]; and during a laparotomy the gut has been pharmacologically shortened in addition. What, then, is the useful meaning to a surgeon during an operation of a "normal" small-intestine length of 22 ft. post mortem? When the resected segment is dead, cold, and stretched, he may estimate from Miss Underhill's figures, but not from his anatomy books, how little gut must be assumed to be left.

This critical approach might well be applied to many so-called "normal" values. Are fluctuations of body temperature around the usual personal value of more clinical importance than the deviation from 98.4° F. (36.9° C.)? Is there such a quantity as the normal weight for a given height and age, or should "normality" of mass be an expression of the proportion of fatty to non-fatty tissue in the body? Independent critical observation and measurement remain as necessary as ever if questions of this kind are to be answered with certainty.

PHILANTHROPY ACCORDING TO PLAN

Less than four years ago, in the new town of Harlow in Essex, two adapted houses were opened as an experimental health centre. Those who attended the ceremony must have felt that, excellent as the provision was, it was wholly inadequate to the needs of the new town which was rising and spreading around it. The report of the Nuffield Provincial Hospitals Trust,[1] covering the period 1951 to 1955, continues the story. The Development Corporation of Harlow planned a new centre to replace this modest unit, together with two additional health centres in other parts of the town. Capital from normal Treasury advances did not materialize, however, and the Nuffield Trust stepped in as a benevolent uncle, seeking an opportunity to demonstrate how, by the use of health centres, a full, varied, and inter-connected range of health services could be economically provided for the new community. Apparently it was desired to avoid the growth of individual practices with isolated surgeries attached to houses. Last year the Trust reserved a capital sum of £70,000 for the purchase of freehold sites and buildings and equipment for three health centres to be used as the headquarters of group practices and also for clinic purposes by the county health authority. Later, in April this year, the trustees reserved another £80,000 to develop three further health centres, and a further £50,000 for special clinics, to be attached to one of these centres, for occupation by the local health authority and the regional hospital board. Now they have reserved yet another £48,000 to build and develop two clinics for use by the industrial health service which is being set up to serve the needs of two industrial estates in Harlow. Thus this most fortunate of the new conurbations will have benefited eventually from the Nuffield Provincial Hospitals Trust by almost £250,000.

Another Nuffield project now proceeding is on quite a different scale, but none the less interesting. On the Channel Island of Alderney, with a population of about 1,400, or perhaps 1,800 in summer, there has been only one small hospital, installed in a nineteenth-century public house, with an operating theatre in what used to be the bar, and with only one bathroom, and that of antiquated pattern, for patients and staff. Some outpatients have had to be seen in the kitchen, and when stretcher cases have been brought in the banisters have had to be taken down and the window opened as a shunting station. No wonder the States of Alderney were perturbed at the possible breakdown of the hospital service. The Nuffield trustees have agreed to make a grant of £20,000 for a new hospital, with the opportunity of experimenting in the design of hospital and health centre facilities for a small and often isolated community. It is hoped that the construction of at least the basic hospital block will have soon been completed.

These are only two examples of the various projects, investigations, surveys, and the like to which the Trust is lending a very generous hand. Another is a grant of £32,000, spread over four years, towards the cost of the experimental two-year training scheme for nurses (in place of the present three-year system) which is being tried out in partnership with the Department of Health in Scotland. A previous job-analysis study of nursing, completed by the Trust in 1953, has in part influenced this experiment. Part of this third report of the Trust describes the completion of past programmes and what has followed from them, and part the projects and inquiries started since 1951. Seldom can so much wise and practical philanthropy have been recorded in so few pages.

[1] *The Nuffield Provincial Hospitals Trust, Third Report, 1951–5*, 1955, Oxford.

CORTISONE IN PRACTICE

BY

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[As we announced last week, on December 5 the Ministry of Health and Department of Health for Scotland are freeing cortisone and hydrocortisone for general prescription by the profession in the United Kingdom. Oral, parenteral, and topical preparations will be available. Corticotrophin (A.C.T.H.), however, will continue to be supplied only through hospitals (see Journal, November 12, p. 1217). We interrupt our weekly series on emergencies in general practice to print this article on cortisone, written by Professor D. M. Dunlop at our request.]

The release of cortisone for use in practice places a powerful weapon in the hands of the medical profession which must be employed with wisdom and propriety. The use of most modern potent drugs carries with it the risk of inducing harmful side-effects. This is particularly so in the case of cortisone, which, besides modifying disease processes, exercises a profound influence on the physical and even the mental attributes of patients. Further, its immediate dramatic and seemingly salutary symptomatic effects in various conditions may tempt the doctor to employ it in circumstances in which its use may be unjustifiable from a long-term point of view. Cortisone is a two-edged weapon, and it is necessary before using it to balance very carefully the beneficial effects which may be expected to accrue against the risks which its use involves. A vast literature has grown up on the subject in the last few years, and there are still wide divergencies of opinion in regard to the efficacy of cortisone in various diseases and its mode of action. Hence it is difficult to do justice to the subject in a short article, which must necessarily be dogmatic and contain generalizations which lack the qualifications necessary for strict accuracy.

In order to appreciate the practical use of cortisone in various diseases it is necessary to make short reference to its more striking effects on metabolism and on the function of different organs and tissues. In the space available it is impossible to discuss these in detail and only the more important applications to clinical conditions are considered.

Physiological Role: Effects on Carbohydrate, Protein, and Electrolyte Metabolism

Cortisone is one of the steroids identified as a product of the adrenal cortex. The action of another steroid—hydrocortisone—is qualitatively similar, although quantitatively hydrocortisone is more potent. The importance of cortisone physiologically lies in the part it plays in the essential maintenance of normal carbohydrate and electrolyte metabolism.

It affects carbohydrate metabolism in various ways. Gluconeogenesis from protein is stimulated so that liver glycogen stores are increased. There is a decreased sensitivity to insulin, so that, when cortisone is given to diabetics, hyperglycaemia and glycosuria are exacerbated. Its prolonged administration to seemingly non-diabetic individuals may very occasionally induce a diabetic state which usually subsides on cessation of treatment. It may be that those who develop glycosuria in response to cortisone are in reality predisposed to diabetes.

By stimulating the conversion of protein to carbohydrate large doses of cortisone induce a negative nitrogen balance, but the increased appetite which it also stimulates usually compensates for this protein catabolic effect. The synthesis of proteins from amino-acids is also impaired, and this may contribute to the slow healing of wounds which has been demonstrated frequently in the experimental animal but which is rarely encountered in the cortisone-treated patient.

Large doses of cortisone cause potassium loss with sodium retention and a consequent tendency to oedema. A low-salt and high-potassium intake is therefore desirable for patients who are likely to require cortisone in high dosage for more than a few days. Under such circumstances 2 g. (30 gr.) of potassium citrate should be given four times a day.

There can be no doubt whatever of the value of cortisone when used as replacement therapy to make good a deficiency, just as thyroid extract is used in myxoedema. Only small doses need then be employed, the hormone being used for its physiological rather than for its pharmacological effects.

Pharmacological Role: Effect on Inflammation and Infections

Apart from cortisone's remarkable action in enhancing the body's response to stress, its most important therapeutic effect is to inhibit the inflammatory reaction of tissues to infective, toxic, or allergic agents. The hormone reduces cellular exudate, diminishes abnormal capillary permeability, inhibits the formation of new vessels and of granulation tissue, and suppresses the fibroblastic reaction of repair. This suppressive action on inflammation occurs irrespective of the primary cause and is entirely non-specific. While the fever and toxaemia accompanying inflammation, which are suppressed by the hormone, may of themselves, if excessive, be detrimental and even lethal, it must be remembered that inflammation is a protective reaction, and that to interfere with this process may be harmful. Cortisone enhances infections of all kinds—pyogenic, tuberculous, and viral—as it allows the parasite to flourish without an immediate reaction on the part of the host. Indeed, the usual evidences of infection may be entirely masked so that they may be overlooked and no remedial measures taken. Further, chronic or dormant pre-existing infections may be aggravated or reawakened.

The administration of cortisone modifies the reaction of the host to certain offending agents, but it has no effect on the agent itself and does not "cure" a single disease. In certain diseases the noxious aetiological agent may persist indefinitely and a return of signs and symptoms follows the withdrawal of the hormone. This "rebound" may take a peculiarly virulent form. Cortisone has therefore to be given indefinitely in such disorders if suppression of their manifestations is to be maintained. Unfortunately the suppressive dose may have to be so large that it cannot be given for long periods without the patient developing undesirable side-effects. This may necessitate the abandonment of treatment, and result in a recrudescence of the disease sometimes in a particularly violent form. Hence in chronic conditions it is not always easy for the doctor to decide whether the use of the hormone is indicated or contraindicated. The decision is not so difficult if a patient is desperately ill and a fatal issue is otherwise likely, or if the inflammatory or allergic reaction is intermittent or self-limiting and the hormone can be given for a short time to tide the patient over a crisis till spontaneous recovery occurs. Further, in the eye, nose, or skin it is often possible to produce a high local concentration of cortisone without any danger of inducing systemic effects.

Effects on Organs and Tissues

Cortisone depresses the function of the adrenal cortex, causing failure of its hormonal secretion. Cessation of treatment is followed by a resumption of cortical activity, but if treatment has been prolonged this may take time to occur. In such circumstances the dose of cortisone should be reduced by stages before it is finally stopped, or it should be followed by a course of corticotrophin for some days to galvanize the dormant cortex into activity once more.

Intensive cortisone treatment may cause hirsutism of the face and body, loss of scalp hair, acne vulgaris, and purple striations, which are all manifestations of Cushing's syndrome. There are also an accelerated blood flow in the skin capillaries, increased skin temperature, and sweating.

The most important effect of cortisone on bone is a tendency to cause osteoporosis which may occasion collapse of the vertebrae in elderly patients undergoing prolonged treatment with the hormone.

As hypertension is a characteristic of Cushing's syndrome it was feared that cortisone might produce hypertension even in patients with a normal blood pressure. Though these apprehensions have not been realized as fully as was expected it is essential to employ cortisone with great circumspection in patients suffering from hypertension or heart failure in view of its sodium-retaining properties.

Most patients develop some degree of euphoria on starting treatment, and this may be of advantage in counteracting the depression of toxic states. On the other hand, cortisone exaggerates neurotic, psychotic, or epileptic tendencies and should be employed only for very compelling reasons in those with an unstable mental background.

The secretory functions of the stomach are stimulated by cortisone, which exacerbates the symptoms of peptic ulceration and may cause haematemesis. Perforation of peptic and colonic ulcers—particularly gastric ulcers—occasionally results from such treatment, and as the signs and symptoms of the resulting peritonitis may be masked the diagnosis is rendered particularly difficult.

Some signs and symptoms of hypercorticism are unavoidable if large doses of the hormone are given for a long time—particularly the moonface. By using a smaller dose, however, it is often possible to achieve considerable though not complete suppression of the manifestations of the disease while avoiding the more serious repercussions of hypercorticism. When cortisone is needed to save life the contraindications to its use become relatively unimportant. Further, the dangers may be much reduced if specific treatment of the underlying disease is given coincidently—for instance, antituberculous chemotherapy in a patient with a tuberculous history, and increased insulin dosage in the case of a diabetic. Nevertheless, the presence or even the history of tuberculosis, peptic ulcer, mental instability, diabetes mellitus, hypertensive cardiac failure, or osteoporosis makes treatment with cortisone unusually hazardous unless it is employed in small doses for replacement purposes. An *x*-ray examination of the chest should be made to exclude pulmonary tuberculosis before starting treatment.

Preparations, Routes of Administration, Dosage

The standard oral preparation is tablet of cortisone acetate (*B.P. Addendum*, 1955) containing 25 mg. of the drug; each tablet costs about one shilling. Injection of cortisone acetate (*B.P. Addendum*, 1955) is a suspension of cortisone in saline (25 mg. per ml.), for which the only suitable route of administration is by intramuscular injection. In general, cortisone is best given by the mouth, the chief exceptions to this rule being found in the case of patients who are vomiting, comatose, or under general anaesthesia. The hormone acts more quickly and for a shorter time when it is swallowed than when it is injected, and the interval between successive doses should be six hours. When given by injection the effect lasts for twelve to twenty-four hours and the equivalent daily dose is about 20% less than the oral one.

The other important adrenal hormone preparation is hydrocortisone. It differs chemically from cortisone only in slight changes in the structure of the steroid molecule. The action of both hormones is similar, but the effect of hydrocortisone is more potent. It is obtainable in solution in 50% alcohol in 20-ml. ampoules containing 100 mg. of the hormone and costs 11s. 9d. an ampoule. It should be used for intravenous administration in acute conditions of adrenocortical insufficiency. The most effective way to use it is to dilute the contents of an ampoule in 500 ml. of isotonic glucose or saline solution, which is then given by intravenous drip infusion. Hydrocortisone has also been usefully employed locally by intra-articular injection, in the form of nasal drops or eye-drops (1% solution), or incorporated in an ointment containing 2.5% of the drug.

The dosage of cortisone is a matter for individual adjustment. The condition is usually brought into remission with initial amounts of 100 to 300 mg. daily, after which the dose is gradually reduced to the minimum maintenance level at which useful, if not complete, control of symptoms can be achieved without producing excessive side-effects. The upper limit of dosage which is unlikely to be accompanied by side-effects varies from patient to patient. It may be taken as fairly certain, however, that side-effects will ultimately be produced by prolonged treatment with daily doses exceeding 75 mg.

Therapeutic Use in Various Diseases

To Induce Hypercorticism

Rheumatoid Arthritis.—Though the remarkable clinical effects of cortisone were first demonstrated by its ability to suppress the functional disability induced by rheumatoid arthritis, and though there can be no doubt that by its use both the local and systemic evidences of the disease can be inhibited, yet it is probable that it has only a limited application in this disorder. Worth-while control of symptoms may not be obtained by a dose of 75 mg. a day, side-effects may still occur even with this dose during long-term treatment, and tolerance appears to increase with advancing age. Further, there is evidence to suggest that the ultimate state of such patients given prolonged cortisone treatment is no better than those receiving adequate doses of aspirin—a far cheaper and less dangerous therapeutic agent. Nevertheless, cortisone may be used with advantage to check rapidly worsening destructive disease in patients who have failed to respond to ordinary treatment or to facilitate certain stages in physical therapy or rehabilitation. The most suitable cases are those in which functional disability exceeds anatomical joint damage. *The more conservative methods such as adequate rest, aspirin, and physiotherapy should always be tried first, as these will produce remission in at least 50% of cases. The same remarks apply to treatment of ankylosing spondylitis by cortisone.*

Collagen Diseases.—Whatever may be the aetiology of the tissue damage in diseases such as disseminated lupus, polyarteritis, temporal arteritis, dermatomyositis, and scleroderma, there is clear evidence that cortisone modifies the tissue reactions in such disorders. Since no other treatment will alter the course of these grave diseases, the same arguments as have been advanced against the routine treatment of rheumatoid arthritis by cortisone should not be applied to them. Hormonal treatment may be life-saving during the acute episodes and may occasionally tide the patient over his illness until an admittedly rare spontaneous remission occurs. Perhaps systemic lupus gives the most gratifying response, particularly when treatment is given before renal involvement occurs.

Acute Rheumatism.—It is possible by cortisone treatment to suppress pyrexia, pain, and swelling in the joints throughout the course of an attack of rheumatic fever, which is a self-limiting disease lasting for a few weeks, and seldom longer than two months. Such treatment does not prevent recurrent attacks in the future, and some time must elapse before it is known whether it will reduce the incidence of valvular damage. It is questionable whether cortisone is

more effective than salicylates in suppressing the symptoms of acute rheumatism, and it is possible that both operate in a somewhat similar manner. Cortisone may be the more powerful drug of the two, but, in the absence of definite evidence that its employment reduces the incidence of valvular damage, its use, either alone or in combination with salicylates, should be reserved for the most severe progressive cases which cannot be adequately controlled by salicylates, and especially when pericarditis is present, as this is often dramatically relieved by cortisone. On occasions it must be confessed that cortisone is ineffective in the control of the rheumatic process.

Sarcoidosis.—This granulomatous condition may be benign and may not significantly affect the health of the patient, so that no treatment is necessary. On the other hand, it may cause serious illness and even death. Clinical improvement can be obtained in a number of such cases by the use of cortisone, which gives more consistent results than any other therapeutic measure. It acts by preventing the formation of granulomatous tissues in the early stages before irreversible pulmonary fibrosis and emphysema have resulted.

Allergic Diseases.—The response to cortisone of asthma, hay-fever, perennial rhinitis, atopic eczema, exfoliative dermatitis, serum sickness, urticaria, angioneurotic oedema, and drug sensitivities is usually rapid and favourable, and may be life-saving. Nevertheless withdrawal always leads to a return of symptoms unless the offending allergen is no longer operative or unless spontaneous remission from natural desensitization has occurred. Many allergic manifestations may be comparatively trivial or may respond rapidly to traditional treatment with sympathomimetic or antihistamine drugs. Cortisone is of particular value for patients dangerously ill with resistant status asthmaticus, in whom it may prove life-saving, and for patients with chronic disabling asthma who have failed to respond to orthodox treatment. Such patients may often be enabled to live satisfactory lives by the daily administration of small doses of cortisone. It may be that it is in this common condition that hormonal treatment will have its most widespread application.

Blood Diseases.—Cortisone has been increasingly used in the treatment of blood diseases during the last few years, but only in acquired haemolytic anaemia of the auto-antibody type, in idiopathic thrombocytopenic purpura, and in acute leukaemia have favourable responses been obtained with any regularity. The hormone should be the primary treatment in both the former diseases. Splenectomy should be reserved for those patients who show no sign of a remission as the result of hormone therapy or who relapse when the administration of the drug is discontinued. In the latter circumstances splenectomy plus cortisone treatment may be effective. There is no doubt that a remission may be induced frequently in acute leukaemia by the use of full doses of cortisone, but it is rare for such remissions to last for longer than three to six months in spite of maintenance treatment.

Ulcerative Colitis.—A considerable subjective improvement with gain in appetite and reduction of diarrhoea often follows the use of cortisone in this condition. Objective improvement has been less striking, but in those patients in whom diarrhoea is most diminished sigmoidoscopic examination usually shows a decrease in the inflammatory reaction. The effect is particularly dramatic in patients suffering from their first attack. Cortisone seems to be much less effective in disease of long standing in which permanent organic changes in the bowel have taken place, but even in these cases hormone therapy may be a valuable pre-operative measure, and critically ill, exhausted, or debilitated patients may thereby be improved enough to permit of elective surgery.

Nephrosis.—The aetiology of nephrosis is unknown, and the means by which cortisone sometimes improves the condition is still debatable. Nevertheless there is no doubt that after a short intensive course of the hormone a free diuresis and a diminished protein loss often ensue when it is suddenly withdrawn. The ideal dosage and length of treatment remain to be determined, but the administration of 100 to 300 mg. of cortisone daily for five to fifteen days is usually recommended. The course is repeated at intervals depending on a return of the oedema.

Dermatological Conditions.—The beneficial use of cortisone in suppressing manifestations of atopic eczema has been already noted. Its use, however, is justifiable only in severe, extensive, and disabling examples of the disease in which the alternative is a prolonged and tedious treatment entailing considerable inconvenience and incapacity. Hydrocortisone ointment is useful in infantile eczema, neurodermatitis, and pruritus ani and vulvae, but as it is very expensive it is unsuitable for widespread application, and in any case its use should be restricted to cases which have failed to respond to other local and general measures. Cortisone is the only drug which will control satisfactorily pemphigus vulgaris, vegetans, and foliaceus. It should be given to suppress the crises of these diseases, in which its use may be life-saving.

Ophthalmological Conditions.—One of the most promising fields for treatment with cortisone has been found in ophthalmology. It can often be used topically in the form of hydrocortisone eye-drops without any danger of producing systemic effects, and it has the ability to block the inflammatory phase not only of allergic ophthalmic reactions but also those due to bacterial and toxic agents. Administration seems, therefore, to be ideally indicated in acute iritis and iridocyclitis, in which, unless the inflammatory process is promptly checked, serious consequences such as cataract and glaucoma may occur. Many other ophthalmological conditions respond favourably to cortisone, but specialist advice should be obtained before its use.

Replacement Therapy

When cortisone is used as replacement therapy it should be remembered that endogenous adrenocortical output is lacking, and the patient is thereby rendered peculiarly sensitive to stresses and infections. It is therefore important to ensure that once treatment is started it is continued indefinitely, and that supplementary cortisone should be given during any intercurrent illness or infection.

Addison's Disease.—This is an incurable disease and treatment must take the form of permanent replacement therapy. Fortunately in deoxycortone acetate and cortisone we now have two synthetic steroids which enable this replacement to be undertaken satisfactorily—the former correcting the disturbed electrolyte metabolism of the disease and the latter combating the hypoglycaemia and failure to resist stress which also characterize it. For maintenance purposes only small daily doses of cortisone are necessary of from 12.5 to 25 mg., though in crises large doses of intravenous hydrocortisone should be given. Cortisone has been so successful in improving the prognosis for such patients that many believe that injections or implants of deoxycortone are now superfluous and that sole reliance can be placed on oral cortisone. Under these circumstances rather larger daily doses of from 25 to 50 mg. are necessary, but it is my impression that a small replacement dose of cortisone and an implant of about 300 mg. of deoxycortone is still the preferable form of treatment for most cases.

Bilateral Adrenalectomy.—Since the introduction of potent replacement therapy bilateral adrenalectomy has become a practical procedure for patients suffering from metastatic cancer of the breast or prostate or from malignant hypertension. Cortisone is given as follows: 200 mg. on the day before operation, 300 to 400 mg. on the day of operation, 200 mg. on the day after, gradually reducing the dose on succeeding days depending on the condition of the patient. The ultimate maintenance treatment is the same as for Addison's disease.

Hypopituitarism.—Remarkable improvement occurs in hypopituitarism as the result of permanent treatment with cortisone. Patients who may have been in a practically dormant, hibernating condition for years can thereby be

restored to a relatively normal life. The dose used approximates to that required in Addison's disease. In addition the replacement of other hormones, defective from the lack of trophic stimuli from the pituitary, is usually necessary.

SIR HENRY DALE, O.M., F.R.S., ON HUMANITY'S RISING DEBT TO MEDICAL RESEARCH

In his Stephen Paget Memorial Lecture on November 17, 1955, Sir Henry Dale said it was more than twenty-four years since he had lectured to the Research Defence Society in commemoration of its founder. He had very precious memories of Stephen Paget's most endearing personality, and especially of the selfless devotion with which in his later years he had given the whole of his effort and interest, sacrificing his health and, in the end, his life to the defence of medical research. Paget had no personal or professional advantage to gain in founding the Society. He was inspired by a strong passion for the truth, and by a hatred for what he recognized as an essentially cruel attack upon scientific researches more directly humane than most in their aims as well as in their results. Paget toured the country in 1914 to counteract the attempt to persuade the men of the new armies to refuse the protective inoculation against the enteric fevers. That particular cruelty was defeated, so that there was no repetition of the tragedy which had overtaken the armies in South Africa for lack of such protection.

Prevention of Diphtheria

Medical knowledge, Sir Henry continued, had owed essential features of its permanent structure to experiments involving the use of animals ever since William Harvey laid its first scientific foundation; and to-day it must become ever more difficult to accept any effective service from medicine without accepting at every turn the applications of knowledge directly arising, or less directly derived, from such experiments. When he had lectured to the Society in 1931 the results of the active protection against diphtheria and tetanus by inoculation with the inactivated toxins of the respective bacteria were not yet available for citation. Only a few years later, however, convincing evidence of the success of the inoculation against diphtheria could have been presented. The record of its application in Hamilton, one of the larger cities of Ontario, was one which was early made available. In 1925 the systematic inoculation of children was begun, and the effect was dramatic. So steeply did the curve fall that after 1930 there were no more deaths from diphtheria in Hamilton, and after 1933, when the inoculation had been in effective action for eight years, no more cases. This achievement was repeated in one after another of such centres of population on the North American continent, leaving no room for doubt that wherever the preventive inoculation of children could be fully applied and maintained diphtheria could be completely abolished. It was not till 1940 that our own Ministry of Health found it practicable to inaugurate a full-scale undertaking, with the preventive inoculation of all children as its aim; and this was not fully under way till 1942. Immediately, however, the enemies of medical research launched a counter-campaign to induce timid mothers to refuse the protection for their children. Their effort was less successful than might have been feared, or than they must be supposed to have hoped. In 1940 there were still in England more than 45,000 cases of diphtheria, and more than 2,400 of these were fatal. Then, with the inoculation becoming effective, the numbers fell steeply and steadily, until in the last full year, 1954, there were only 173 cases, and only 9 deaths from the disease. Of the nine deaths recorded in 1954 six were in children under 15, and all of these occurred in the minority who had not been inoculated; and among all the children of any age who had received the inoculation within the last five years there were no deaths in 1954.

Tetanus in the Second World War

The value of preventive inoculation against tetanus was a more recent discovery. Fortunately the arrangements had been made in advance for this active immunization of the armies of the second world war. Here again, however, there was an organized effort to persuade the soldiers to avail themselves of a legal right to refuse this protection. The British Expeditionary Force, which was brought back from Dunkirk in 1940, had fought a gruelling rearguard action over soil which experience had shown to be highly dangerous as a source of the tetanus infection; and they had been transported home under conditions which made inevitable a long delay in the cleaning and dressing of their wounds. Yet, in the more than 16,000 wounded in that army, there were only seven cases of tetanus; and these were all in men of the 10% who had been persuaded to refuse the protective inoculation; among the 90% who had been inoculated there was no tetanus. And so the records continued for the rest of the war. Those for the Mediterranean campaign gave an opportunity for comparing the experience of the South African troops, who had not been inoculated, with that of the Australian and British troops, who had. Among less than 4,000 South African wounded there were five cases of tetanus, while among more than 8,000 Australian wounded there were none, and among more than 27,000 British there was only one, in a man whose immunization was doubtful. In so far, then, as the campaigns of persuasion to refuse inoculation had been successful those who had conducted them could not escape the responsibility for agonizing deaths of children in diphtheria, and of soldiers in tetanus, which could clearly have been prevented.

It was now more than thirty years since those then working in the National Institute for Medical Research had been asked by the Medical Research Council to take part in research on the problem of the diseases due to the so-called ultramicroscopic viruses. They chose dog-distemper for investigation. In due course Sir Patrick Laidlaw and Mr. Dunkin elaborated a method of preventive inoculation which was not only effective in protecting dogs from distemper but, since it broke new ground, gave a lead in certain directions to the search for methods of immunization against other diseases due to virus infections, of men as well as of other animals. The method of conferring immunity against distemper was greatly improved and simplified, so that the material for the inoculum, or vaccine, now successfully used for immunizing dogs, was no longer obtained from infected dogs and ferrets but from cultures of the virus on incubated eggs containing chicken embryos. But from the time the preventive treatment first became available, even to the present day, there had been a persistent campaign to induce owners to refuse the protection for their dogs.

Specific Chemotherapy

Sir Henry Dale then reviewed some of the advances in medicine since 1931. "You cannot, in fact, move anywhere in modern medicine without the use of knowledge produced by experimental researches, in a large proportion of which it has been necessary to make some use of experiments on living animals." In his lecture of 1931 his only reference to a specific, chemotherapeutic remedy for an infection was to "salvarsan." Ehrlich's earlier attempt to discover a specific remedy for an infection had been halted for many years. As early as 1891 he had experimented on the possibility of treating malaria in man with methylene blue. Some thirty-five years later it occurred to the research workers of the Bayer Company, in Elberfeld, that the malaria-like infections of certain small birds could be used for a preliminary trial of substances for an antimalarial action. These malaria-like blood-parasites of birds had helped Ronald Ross, many years earlier, to recognize a mosquito as the natural transmitter of malarial infections. They were able, by tests on such artificially transmitted infections in small

birds, to select, for successful trials on naturally acquired malaria in man, the remedy which they called "plasmochin" and then another which they called "atebrin." The latter was called mepacrine in this country; and its production here in the second world war came just in time to save the situation for our armies in Burma and New Guinea, when the Japanese, by invading Malaya, had seized the world's main source of quinine. And then, during the war and in the years following, malaria-like infections in domestic poultry, and then in mice, were found and pressed into service, with the result that other and better antimalarial remedies became successively available. So the use of experiments on animals in the search for new and better remedies for malaria had produced a position in which an adequate organization of the world's resources, using the effective antimalarial remedies now to hand, together with the potent available insecticides, ought to be able to rid the world of malaria; and malaria was still, he supposed, the greatest single cause of mortality and chronic ill-health to a large proportion of the world's peoples.

In 1935 Professor Domagk, in Elberfeld, found the right kind of septicaemic infections in mice for the testing of potential remedies and a synthetic substance which, when so tested, was found to have a clear therapeutic action; this proved to be the starting-point for the now long series of sulphonamide remedies. The prospect of sufferers from child-bed fever and other septicaemias, from pneumonia and cerebrospinal fever, and, when the war came, from bacillary dysentery underwent a dramatic improvement. Meanwhile Sir Howard Florey, with Professor Chain and others in Oxford, in the course of a new kind of survey, undertook a thorough examination of the curative potentialities of penicillin, which the late Sir Alexander Fleming had discovered some ten years earlier. When Sir Alexander Fleming died in the spring of the present year the whole world was united in mourning the loss and honouring the memory of the man whose genius for alert and accurate observation had enabled him thus to write the essential opening paragraph of this new and glorious chapter of life-saving, scientific knowledge. It was very important, however, that everybody should be made to understand that Fleming's discovery, so rightly recognized and acclaimed, might have remained indefinitely without the practical applications which had meant so much to mankind if Florey and his team had not made a new and thorough investigation of the properties of penicillin as an internal antiseptic with the help of an adequate series of experiments on living animals.

Sir Henry Dale concluded his lecture with an appeal to his audience to join Stephen Paget's Research Defence Society.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Ban on Heroin

SIR,—The ban on heroin is to stay. The Home Secretary, who promised the B.M.A. deputation to reconsider the matter, has presumably done so. The attitude of the Home Office and the Ministry of Health has been consistent—namely, that having consulted the standing medical advisory committees they could not do otherwise than accept the advice of such eminent men. Up to a point, that is to say until the views of the medical profession became obvious, they cannot be criticized. The primary blame for this unwise edict rests with the medical members of the advisory committees. Since then, however, a flood of protests has reached the Ministers in the medical and lay press, in a deputation, and in letters from the entire professional staff of at least eleven of the largest hospitals in London, and from hospitals in the provinces. It must now be abundantly clear to the Ministers concerned that the medical profession as a whole condemns this restriction on clinical practice. Is it possible that face-saving is more important than alleviation of suffering?

Hardship to patients involved by the banishment of heroin can be postponed for a few years by the laying in of stocks. Many hospitals have already done so. The tragic failure of the measure to check heroin addiction is inevitable. It is as unavoidable as was the drunkenness which followed prohibition in the U.S.A., and the increase in heroin addiction consequent upon the drug's ban in 1925 in that country. The outstanding lesson of this controversy is that the structure for consultations between the Government and the medical profession is faulty. The matter must not be allowed to rest.—I am, etc.,

London, W.1. A. H. DOUTHWAITE.

Guidance and Didacticism

SIR,—The clarity of thought shown in your two recent articles on anaesthesia ("Contraindications to Thiopentone Anaesthesia," *Journal*, October 1, p. 836, and "Hypothermia," *Journal*, November 5, p. 1131) is admirable and of great assistance to anaesthetists. May I, however, utter a word of protest against the tendency to authoritarianism evident in both articles, and particularly in the latter? It has always been considered fair game for anyone in medicine to lay down the law concerning anaesthetics, but it is particularly regrettable that you, Sir, should join in the chorus. Guidance we expect and appreciate: but the danger of this straying into didacticism lies in the popularity of litigation and the tendency of counsel to regard articles such as yours not in the light of guidance and informative opinion but rather as the final and unalterable laws of medicine, departure from which is to be regarded as negligence.

For instance, few of us would not agree that your list of contraindications to thiopentone anaesthesia is comprehensive and complete. Yet, surely, many on reading the article must have reflected that on the rare occasion they have been impelled to violate the immediate safety rule for the ultimate benefit of the patient. It would be a sorry day when the fear of litigation encouraged by dogmatism in the journals should make the anaesthetist afraid to take such a step if convinced of its necessity. Furthermore, the logical extension of one of your statements is untenable. If it is unwise to take the patient from ward to theatre while unconscious, surely, then, each case should stay in the theatre until consciousness has been regained. I leave it to your imagination to picture the effect of this upon the duration of operating lists.

It is, however, in your article on hypothermia that you make the intolerable statement. After an admirably erudite dissertation of the uses of hypothermia, you say: "It should not be practised outside the few major hospitals with experience of this type of work." With all respect, I disagree absolutely and completely. The statement amounts to a belittlement of work done outside these chosen "few"; it denies to other hospitals the benefits of hypothermia; and, as a corollary, it precludes the initiation of specialized surgery likely to benefit from hypothermia, other than in hospitals already among the chosen ones.

Having said as much as you have, I suggest it is up to you now to name the "few major hospitals," which, like the Lord High Executioner, you have on your little list. I trust you will agree that this is tantamount to a direction of work emanating from the editorial office of the *British Medical Journal*—which I submit is no part of your function. As yet there is no post of D.A.S. (Director of Anaesthetic Services) in England; and I can see no valid reason for your tendency to assume this cloak.—I am, etc.,

London, S.W.15. G. C. STEEL.

Anticoagulants and the Prothrombin Pattern

SIR,—Dr. H. L. Matthews and his colleagues (*Journal*, October 15, p. 947) have presented a valuable and interesting study of the pattern of "prothrombin times" over the 24 hours in patients receiving maintenance doses of phenindione and ethyl biscoumacetate, but it is unfortunate that they have expressed their results in the form of "prothrombin concentrations" instead of "prothrombin times." Both terms are, of course, misnomers, since Quick's test measures the activity of factor VII in addition to that of prothrombin, but the publication of the actual "prothrombin time" would be much more informative. The "prothrombin concentrations" may have been arrived at by expressing the normal "prothrombin time" as a percentage of the patient's "prothrombin time." The more usual term for this figure is "prothrombin index," but this term really has little to commend it.

One would more readily presume that the "prothrombin concentrations" have been calculated from the "prothrombin times" using a dilution curve for normal plasma, and an analysis of the authors' graphs on this basis is revealing. The apparently dramatic fall in the ethyl biscoumacetate graph in Fig. 1 from a concentration of 44% to 32% (approximately) represents a difference of only about 4 seconds in the "prothrombin time," and in this range the *experimental error alone* is of the order of 2 seconds. Lesser deviations on the graph then assume even less significance. Since the "prothrombin times" during phenindione therapy were rather more prolonged, the graph for phenindione would not be so misleading, and the fall from the fourth to the eighteenth hour would represent approximately a 6-second difference in "prothrombin times." The authors' conclusions may well be valid, but a few words of explanation would avoid ambiguity and enable us to confirm their conclusions.

Lest this whole argument appear a mere quibble over terms which are almost synonymous, may I be allowed, in the interests of lucidity, to suggest that in reports and publications on anticoagulant therapy the terms "prothrombin concentration" and "prothrombin index" be avoided and that the straightforward "prothrombin time" be used (the alternative use of the expression "prothrombin-factor VII activity" is hard on the tongue and the brain). This simplicity increases in importance as more and more doctors with little or no laboratory experience use anticoagulant therapy and attempt to understand their laboratory reports or the publications in the literature.—I am, etc.,

Aberdeen. T. B. BEGG.

Acute Phlegmonous Caecitis

SIR,—Mr. F. Baar is to be congratulated on the successful outcome of his case (*Journal*, October 15, p. 948), which survived in spite of advanced peritonitis and diabetes. Owing to the necrotic state of part of the caecum, the piece excised was apparently unsuitable for a detailed examination and obviously quite unsuitable for histological study.

From the list of differential diagnoses considered it is apparent that the writer is unaware of the condition of solitary diverticulitis of the caecum which occurs in young adults and is, prior to operation, indistinguishable from acute appendicitis. Gangrene and perforation are specially liable to occur if a perforation is present. At operation the condition is often widely excised, as it simulates a perforated carcinoma. I have seen six cases, and most surgeons with an extensive experience of acute abdominal conditions have encountered the condition, which has been frequently recorded in the literature.

I therefore think that Mr. Baar's case was probably of a similar nature, and I doubt whether there is a separate clinical condition of idiopathic acute phlegmonous caecitis.—I am, etc.,

Liverpool, 1. M. J. BENNETT-JONES.

Cerumenolytic Agents

SIR,—I have just received the *Journal* of October 8, and have read Mr. J. Rabinovitch's letter (p. 911) with interest. The reason which he gives for the failure of "cerumol" in the clinical trial is not entirely convincing. However, should his theory of adsorption of the preparation on the cotton-wool be partially, or even entirely, correct, it does not nullify the results obtained but merely gives an explanation for the failure of cerumol in clinical practice. As colleagues have remarked, it is necessary to plug the external auditory meatus to prevent the cerumenolytic dripping out.—I am, etc.,

Cambridge, Mass, U.S.A. R. HINCHCLIFFE.

Lipids and Atheroma

SIR,—It has been suggested that a high fat diet is an important factor in the aetiology of coronary thrombosis (*Journal*, October 22, p. 1016). J. T. Ireland and myself investigated this problem some years ago.[1] It is well known that arterio-sclerotic patches contain cholesterol, and Antischkow[2] has produced in rabbits arterio-sclerotic changes by feeding them with cholesterol. It is perhaps significant that so far all attempts to produce arterio-sclerosis by this means in carnivorous animals have failed.

We have established that the amount of cholesterol in the serum depends on the capacity of the blood to hold cholesterol. This capacity depends on a number of factors. We found by administering to human beings a high protein diet for more than five weeks the level of the serum cholesterol rose. Bleeding, too, produces a rise in the serum cholesterol. On the other hand, injection of cholesterol did not raise the serum cholesterol. There was no consistent rise of cholesterol on a high fat diet. We found, however, that the total serum-fat is increased in hypertony.[3] We have established that, particularly in the middle-aged, there is a large retention of nitrogen (protein) on a high protein diet,[4] which would automatically increase the capacity of serum for holding cholesterol in solution. We have also established by feeding rabbits on high cholesterol there is an increase in the capacity of the blood for holding cholesterol by mobilizing fat in the blood. But this only applies to rabbits. We may take it that a high fat intake by itself does not give rise to arterio-sclerosis or coronary thrombosis. My own belief is that the excitation cause of thrombosis is a lowering of pressure in the coronary circulation below requirement (coronary failure) as a reaction of a sudden increase of pressure in the aorta. In one of the latest victims under my observation coronary thrombosis developed as the result of a fright—while opening an electric stove a white mouse made its appearance—and the number of heart attacks due to sudden emotional strain is such that we must attribute to it some significance.

It would be interesting to know the experience of your readers with regard to the excitation cause of coronary thrombosis; the age of the patients who exhibit coronary trouble; and whether there is a history of hypertony; also the incidence of recovery in relation to age.—I am, etc.,

Liverpool, 1. I. HARRIS.

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Clinical Teaching

SIR,—Miss Beryl D. Corner in her letter (*Journal*, September 24, p. 789) puts her finger on the weak spot of our profession—the doctor's education. Among remedies she warmly advocates team-teaching of students in hospitals. Sharing as I do her concern that staff and student feel things are sadly awry, may I suggest two other steps in reform?

First, it is a pressing duty to restore to seemly proportions the undergraduate curriculum, which has rapidly grown monstrous. As for postgraduate education, the need for this looms large not only among general practitioners but also among consultants, whose numbers have doubled since the war. Constructive planning is wanted in our specialties. Secondly, since clinical professors have become vastly overburdened, the time is ripe for dividing the duties of the chair between two professors, one being responsible for the academic and scientific aspect, the other for pedagogy in the clinical sphere.

Towards the first reform, may we ask the G.M.C. to request from teaching bodies a radical revision of the curriculum, retaining only what is proper to one qualifying as a family doctor (not a multiple specialist) and what the brain of the average student can absorb? In the urgent problem of providing efficient postgraduate facilities, London has led the way with the Institute at Hammersmith. Numbers may not justify a separate hospital in the provinces, but is it not the duty of each teaching hospital to cultivate courses in the various specialties? The Health Service would doubtless support sabbatical leave to consultants scattered throughout the corresponding hospital region, to enable them to keep abreast of current advances. The onus is on the teaching hospital, as the academic nucleus of its region, to organize the work. The G.M.C. is needed to ensure a good qualifying standard in general practice; what about a similar regard for the public interest at consultant level? Is it enough, where human suffering is at stake, to guarantee proficiency at the outset of a career and leave to chance the maintenance of an up-to-date competence?

Secondly, granted the G.M.C. gives its blessing to such radical reforms in education and training, how can they be put into effect? Surely by a new teaching appointment wholly devoted to clinical pedagogy in the main divisions, medicine and surgery, for the duties of clinical professors have already become too ponderous in bulk and diversity. Many new factors create the present dilemma confronting organizers. Thus, since the war undergraduates are twice as many and the new postgraduate group has become formidable. Clinical science and techniques increase and change like a kaleidoscope; these not only absorb time in practice but necessitate revised curricula and planning anew. The latest distraction is meteoric air travel now carrying our academic leaders to centres across the continents on visits of weeks or months. The life of clinical professors is harder, anyhow, owing to the absence of vacations in hospital work, and because pedagogic duties demand their vigilant supervision of students engaged in the relief of suffering.

Clearly, if to the overburdened is added the development of the postgraduate section of education here envisaged, the chairs of clinical medicine and surgery each will need sharing by two professors with different bents. Thus, in medicine, the academic post calls for a brilliant clinician, thinker, and leader in research; whereas, when choosing one to be in charge of pedagogy, surely the outstanding qualifications would be a gift for teaching and discipline; this professor would need to be *persona grata* among his colleagues, the teaching staff in both undergraduate and postgraduate sections. Let me close with a Latin quotation—"*Tempora mutantur, nos et mutamur in illis.*"—I am, etc.,

Bristol, 8. A. WILFRID ADAMS.

Training of Spastic Children

SIR,—Mr. Vosper, of the Ministry of Education, has said it was a false kindness to suggest that handicaps suffered by spastic children could be completely overcome or that all the children could be enabled to lead a normal life (*Journal*, October 22, p. 1025).

The National Spastics Society has never made any suggestions of this kind. We do, however, encourage parents to have faith, and we do not accept that because no solution has been found none ever will be. Many afflictions once deemed hopeless have now been conquered.

Professor Capon has said that the service for spastic children was too complex and impersonal, with a host of specialists. That is why we have been fighting for schools and training facilities, a number of which we ourselves have now opened, thanks to the public's generosity.—I am, etc.,

London, W.1. IAN R. HENDERSON, Director-General, National Spastics Society.

Serum Amylase and Acute Abdominal Disease

SIR,—I should like to comment on several points raised by Dr. R. F. Bolam in his letter (*Journal*, October 29, p. 1086). In discussing the occasional high values of serum amylase found in cases of perforated peptic ulcer which Dr. T. D. Ness and I reported (*Journal*, September 24, p. 770), he states that "in such cases radiography of the abdomen would not fail to reveal the presence of intraperitoneal gas." This, unfortunately, is not always true. The demonstration of gas is conclusive evidence of perforation in a suspected case; the absence of such gas means nothing. Even under good conditions it is sometimes not visible, as much fluid but little gas may have escaped through the perforation. Further difficulties may also arise when the radiographs have to be taken with portable apparatus, and the patient is unable to co-operate fully because of his severe pain.

Dr. Bolam feels that our statement that serum amylase levels may be used to differentiate acute cholecystitis from acute pancreatitis is based on wrong premises because there are all gradations of acute pancreatitis from mild to severe, and both acute cholecystitis and pancreatitis can occur together. He considers that this may happen more frequently than is thought. With regard to acute pancreatitis we were concerned with patients who had severe upper abdominal pain and were seriously ill. Under these circumstances, it was felt that the term "acute pancreatitis" was justified, and the level of serum amylase found was invariably very high as opposed to that found in cases of acute cholecystitis, who were also ill patients. Concerning the concomitance of the two diseases, acute cholecystitis was found in only 2 out of 19 cases of acute pancreatitis submitted to laparotomy in the acute phase during the last 6 years in this unit. It would seem that biliary tract disease is only one of the many factors involved in the pathogenesis of acute pancreatitis.

Finally, elevation of the level of serum amylase does not necessarily imply the presence of pancreatitis; increased values of pancreatic origin may be demonstrated, for example, by morphine-induced spasm of the sphincter of Oddi during a phase of active pancreatic secretion, and may occur in renal failure where elimination of pancreatic amylase from the plasma is lower than normal. Another example of excess pancreatic amylase in the blood without pancreatitis is found in perforated peptic ulcer, where the amylase escaping through the perforation into the peritoneum is absorbed to a degree probably determined by the extent and duration of contamination. The minor elevations which we reported in acute cholecystitis, appendicitis, urinary infection, etc., remain unexplained; as part of a current investigation into the types of amylase present in the body, we hope it may be possible to determine whether these elevations are due to an amylase of pancreatic origin or to the absorption of bacterial amylase.—I am, etc.,

Aberdeen. WILLIAM BURNETT.

SIR,—In his letter under this heading Dr. R. F. Bolam (*Journal*, October 29, p. 1086) has drawn attention to the interesting association of acute cholecystitis and acute pancreatitis. He mentions a patient who "was found at emergency operation 21 months ago to have an acutely inflamed perforated gall-bladder and a swollen oedematous pancreas." The literature contains very few references to the association of these disorders, which cannot be very uncommon. Two cases of biliary peritonitis due to acute pancreatitis have

occurred in my practice, and I am convinced that in some of the reported cases of biliary peritonitis the associated changes of acute pancreatitis have escaped the notice of the observer. The cases have been labelled as "idiopathic."

There is a slight anomaly in Dr. Bolam's letter in that, after quoting the widely held opinion that operation during the acute phase of acute pancreatitis leads to an increased mortality, he says that "all the cases here were treated conservatively." Perhaps the first case was operated upon at another hospital.

One of the reasons for the increased mortality in cases of pancreatitis that have been operated upon is that it is the case with complications that demands operation. If the gall-bladder perforates, the peritoneum and the biliary system must be drained. The mortality of such cases is high, but this is no argument against operation. The patient has a chance of survival by operation; without operation death is certain. If there are signs of peritonitis, and if they spread, laparotomy must not await the result of estimation of the serum amylase.—I am, etc.,

Hove. P. A. LANE ROBERTS.

"Veripaque"

SIR,—Whether veripaque mixed with the barium suspension is of value in the barium enema examination of the colon has not been shown, but we cannot agree with Dr. Norman P. Henderson (*Journal*, September 3, p. 617) that it is of no value in the preparation of the colon for the examination.

In the preparation of patients—only in preparation—we now use veripaque as a routine. 3 g. of the powder are dissolved in 4 pints (2.3 l.) of water. Tap water is as effective as distilled. 3 to 4 pints (1.7–2.3 l.) of the solution are run in through a tube and funnel, using, for patients who have difficulty in retaining the fluid, an inflatable balloon in the rectum. The patient evacuates and then the colon is washed out with water, 2 pints (1.1 l.) at a time, till the fluid is returned clear. Sometimes the first return is clear. Usually three to five 2-pint (1.1-l.) washouts are required.

Out of 50 consecutive patients the colon appeared from the films to have been prepared perfectly—there was no trace of faecal material—in 47, and in 2 of the others the colon was clear up to the site of a carcinoma, though faeces were present above. The only reactions encountered were nausea once and vomiting once. Pain during injection was negligible.

The main advantage of this method of preparation is the great saving of nurse-hours. In almost all these cases the preparation was completed within 45 minutes, in many within 30 minutes. This compares very favourably with the one to four hours required for the ordinary method.—We are, etc.,

W. STACHURKO.
G. OSBORNE.

London, N.19.

Phthalylsulphathiazole in Control of Sonne Dysentery

SIR,—The article on a trial of phthalylsulphathiazole in controlling Sonne dysentery in day nurseries (*Journal*, October 15, p. 939) has added to our knowledge of chemoprophylaxis of Sonne dysentery. Trials of chemoprophylaxis have been carried out in various parts of the country, following a suggestion made by the Ministry of Health in 1950.[1] Each trial has contributed useful information, and the value of chemoprophylaxis with various sulphonamides has varied from trial to trial. My personal opinion is that each outbreak of Sonne dysentery is a distinct epidemiological problem, and that the value of any measure taken to control an outbreak of dysentery is peculiar to that particular outbreak. Having been interested for some years, both in the treatment and prophylaxis of dysentery, I would like to make the following observations.

Contrary to the opinion of the writers of the article in the *Journal*, I firmly believe that a high standard of hand hygiene is extremely important in preventing the spread of Sonne dysentery. *Sh. sonnei* can be isolated from the hands of carriers and objects handled by them. Ordinary washing of the hands in soap and hot water will remove *Sh. sonnei* in practically all cases. Many closed communities, such as residential schools, allow carriers to return to normal school activities,[2] the only stipulation being a high standard of hand hygiene. Secondary cases are very rare at schools where this practice is adopted. In open communities, such as day nurseries, the value of hand hygiene is reduced owing to the possibility of outside infection.

Sensitivity trials *in vitro* with sulphathiazole derivatives appear to be very unreliable, as they owe their activity in the gut to free sulphathiazole resulting from hydrolysis. I have found it better to test a particular sulphonamide by using it to treat cases of dysentery, and if found effective in treatment it is usually also of some value as a prophylactic for the same outbreak. Forbes[3] collected seventeen strains of *Sh. sonnei* belonging to six phage types, and some of these strains, though sensitive to sulphonamides *in vitro*, did not respond to the same sulphonamides when used clinically.

One very interesting observation by the writers of the article is the number of secondary cases following initial high infection and low infection rates. In my opinion, another important factor is whether the outbreak is fresh or has been present for some weeks.[4] When dealing with a fresh outbreak, both treatment and chemoprophylaxis with sulphonamides appear more effective. I have found that chemoprophylaxis is valueless in the control of an outbreak where cases or carriers have occurred over a period of weeks. It would have been interesting, in the investigation reported in the *Journal*, to have taken specimens of faeces from all children at the nurseries before the first case occurred to find whether symptomless carriers were present. If symptomless carriers were present, which is quite possible, results with sulphonamides as prophylactics would be disappointing. When an epidemic has smouldered for some weeks, then antibiotics, preferably streptomycin by mouth, should be used to clear the carrier condition and treat any fresh cases. The time has now arrived when it may be justifiable to carry out trials with streptomycin orally as a prophylactic, particularly in certain circumstances—for example, a children's ward in hospital. There appears to be no objection to using streptomycin as a prophylactic agent, as it is not absorbed from the bowel, is non-toxic, and does not irritate the gastric or intestinal mucosa.—I am, etc.,

Mold, Flints. G. W. ROBERTS.

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C. E. Rhodes Fund

SIR,—The medical profession will have noted with pride the posthumous award of the Albert Medal to the late Surgeon Lieutenant Charles Eric Rhodes, R.N.V.R., as recorded in the *Journal* of November 12 (p. 1218). Eric Rhodes was an enthusiastic member and sometime secretary of the United Hospitals Sailing Club, and the club has started an appeal for funds to help his wife and daughter. A plaque recording his heroism is to be placed in the club-house at Burnham-on-Crouch. Many of your readers may wish to contribute to this appeal. Donations should be sent to me at University College Hospital Medical School, London, W.C.1.—I am, etc.,

M. L. ROSENHEIM,
Hon. Treasurer,
United Hospitals Sailing Club.

Early Diagnosis of Cancer of the Cervix Uteri

SIR,—The article by Dr. Malcolm Donaldson (*Journal*, October 29, p. 1081), when dealing with cytological diagnosis of cervical cancer, expresses an opinion on our experience of the method in this country which is widely held but no longer tenable. Here we may not have examined

as many smears as workers in Canada or the U.S.A., but we have shown that the method is not unduly difficult. To my mind it is one that is well within the competence of any experienced morbid histologist and should be considered to be part of his armamentarium. Special centres and specially trained technicians may be convenient in special circumstances, but they are by no means essential for success. We are perhaps more cautious than our transatlantic colleagues in that we do not demand hysterectomy as the result of a smear, but recommend ring biopsy.

At the Women's Hospital, Liverpool, Ayre's smears of the cervix are taken from all women over an agreed minimum age attending out-patient clinics, the exact age at which the minimum is set depending on the preference of the individual surgeon whose clinic the patient attends. Of our last 200 smears, five have been reported as malignant. Of these, three have been confirmed by histology, one awaits ring biopsy, while in one case the surgeon prefers to watch the patient and repeat the smear later. In all these five women no clinical suspicion of malignancy was entertained. In the same period of time as it has taken to collect the 200 smears, 309 cervices have been removed for non-malignant conditions and submitted to section. Among these, one completely unsuspected case of intra-epidermoid cancer was found. The patient had been admitted direct to the private ward for a prolapse operation and no Ayre's smear had been taken.

I feel, therefore, that the Ayre's smear is a useful and not unduly difficult method of diagnosis of early cervical cancer. It is important, however, that a proper perspective should be retained and the method should not be allowed to usurp the place of histology as the final arbiter of malignancy.—I am, etc.,

Liverpool, 1. R. E. REWELL.

SIR,—Dr. Malcolm Donaldson's most excellent article (*Journal*, October 29, p. 1081) on "The Early Diagnosis of Cancer of the Cervix Uteri" has my entire support and agreement. It is lamentable indeed that failure to diagnose this condition in its incipient stages should ever occur, because early warnings are so constantly given and early application of treatment is so hopeful of cure. Surely to-day no medical man would fail to recognize the possible significance of irregular uterine haemorrhage and vaginal discharge, and to institute promptly a full investigation.

Important as is the early diagnosis and treatment of this cancer, there is another essential consideration—the anticipation and prevention of its occurrence. The disease is virtually unknown in non-parous women. As far as can be seen it is reasonable to think that the only ill effect on the cervix uteri which delivery, at any stage of gestation, may have is laceration of this structure. If such a cervix be left untreated, chronic inflammation, hypertrophy, and induration are extremely likely to follow. Such cervices must always be regarded as the particular type in which cancer is likely to develop later. No cervix uteri affected by laceration, inflammation, and induration should ever be left untreated. If there is not complete and satisfactory resolution of the inflammation and return of the cervix to a normal state, then the cervix should be removed in its entirety.

With such care as this, cancer of the cervix should be as rare as the terrible diseases which so devastatingly plagued the world in former years.—I am, etc.,

London, W.1. J. LYLE CAMERON.

Munchausen Syndrome

SIR,—The patient described by Drs. R. A. Gawn and E. A. Kauffmann (*Journal*, October 29, p. 1068) is well known to me. I was asked to see him in January, 1951, when he was giving his usual performance at the Central Middlesex Hospital. At that time my article on the syndrome[1] was about to be published, and I nearly included his case in it but thought that more than three examples would be boring.

There are three varieties of Munchausen's syndrome: (1) the abdominal type (laparotomophilia migrans), (2) the bleeding type (haemorrhagica histrionica), (3) the type specializing in faints, fits, palsies, and other nervous symptoms (neurologica diabolica). This patient is a very fine example of the second type—haemorrhagica histrionica. Whether publishing details about him will help others to recognize his condition at other hospitals is uncertain, because his case has been fairly widely published already, not only by I. A. Short,[2] as mentioned in Gawn and Kauffmann's communication, but also by P. J. Cook, of Ramsgate, A. Greville Young, of the Lister Hospital, Hitchin, and various other doctors who wrote about him in the same issue of the *Lancet*.[3] He does occasionally come to the same hospital twice, and the Queen Elizabeth Hospital, Birmingham, have had this experience. A very full account of him was given in the *Journal of the Irish Medical Association* by Dr. P. B. B. Gatenby.[4]

This patient is probably causing more trouble than almost any other patient with the syndrome, and there must be few hospitals in this country that he has not visited. His visits have not been confined to this country but he has travelled widely in Ireland, France, and on the Continent. It would save a great deal of trouble if he could be certified or if anyone could find out the reason why he has this peculiar desire to wander from one hospital to another with his spurious haemorrhages. An unusual feature of his case is that he uses the same name at every admission, whereas most of these people have a large number of aliases. Another feature of his performances is that very often when picked up he tells bystanders that he was on his way to a monastery. Recently a consultant colleague of mine was rung up at his home by his house-physician, who told him that a young man had been picked up in a dazed condition, collapsed near the hospital with bleeding from his ears and other sites. The only question my colleague asked was, "Was this patient on his way to a monastery?" and the surprised houseman, much impressed by his chief's almost supernatural powers, replied, "As a matter of fact he was." This fact may help others who wish to establish an early diagnosis in this case.

In December, 1954, Drs. I. F. Collie and T. G. Grygier,[5] of Banstead Hospital, Sutton, announced that they were starting "intensive research into Munchausen syndrome" and that this would include "psychiatric and psychological analysis" of these patients. I wrote to them in December, 1954, about this man, to give them a chance to get him under their care, as at that time he was particularly active and had been in Hammersmith Hospital, the Metropolitan Hospital, and Bromley Hospital, but I have heard nothing more about him since then until I saw Drs. Gawn and Kauffmann's recent note.—I am, etc.,

London, N.W.10. RICHARD ASHER.

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SIR,—The recent medical memorandum on a case of Munchausen syndrome by Dr. R. A. Gawn and Dr. E. A. Kauffmann (*Journal*, October 29, p. 1068) could not have been published more opportunely.

On October 27 a patient, giving his age as 23, was admitted to our wards as a case of serious haemorrhagic disease. The features of the case were practically identical with those given in your medical memorandum. The patient gave a long history of bleeding troubles with haematuria, and had had a splenectomy in Paris. He is also under treatment with cortisone. He told us that he was under the care of a physician in Belfast, and gave us a clever story of how the notes of his case history had been unfortunately misplaced.

He ascribed his knowledge of medical details to the fact that he is a telephonist in a hospital and that this post had been obtained for him by his physician.

At the first interview with the patient he struck one as being a pleasant and helpful type of man. It was not until he demanded increasing doses of pethidine that one became suspicious of his personality. He is obviously a pethidine addict, and he demands this drug for classical renal colic. Your article has saved us from further embarrassing and fruitless medical tests on this patient.

In retrospect, he is an intriguing personality. He plays his cards beautifully and none of the gross inconsistencies and errors of the inexperienced malingerer emerge. On being given water instead of pethidine for injections, a fact of which he was well aware, he took his own discharge from Watford. The night following his discharge he was admitted to the West Herts Hospital, where he caused sufficient anxiety to require the summoning of donors for fresh blood. Your article again unmasked him and he was discharged. I gather that on the very same day, six hours later, he made his appearance in a South London Hospital. Further inquiries have led to the fact that he was in two further hospitals during the preceding three days to his admission here.

I only hope that further publicity about this troublesome man will lead to his early detection by those unfortunate casualty officers and house-physicians who have to deal with him.—I am, etc.,

Watford. E. WILSON JONES.

Dangerous Bronchitis

SIR,—The article on dangerous bronchitis by Dr. E. Keith Westlake (*Journal*, October 15, p. 960) in the series "Emergencies in General Practice" should be of great help to practitioners, and his points of differential diagnosis between bronchitis with respiratory failure and left ventricular failure with pulmonary oedema especially so. I do feel, however, that we are occasionally confronted with a case where left ventricular failure with pulmonary oedema occurs as a complication of acute bronchitis in a patient who has a history of chronic bronchitis emphysema and asthma. I have seen two such cases in the past 12 months, the more recent of which was particularly alarming.

The patient, a man of 56 with a history of bronchitis and emphysema for many years, who had been gassed in the first world war, started an acute attack during the recent damp foggy weather. A few days after the onset of the attack I was called to him urgently and found him deeply cyanosed from respiratory failure with all the complications, the worst feature of which was the severe muscular rigidity. The immediate impression was that his cyanosis was due largely to his acute bronchial spasm, but the injection of aminophylline and the administration of oxygen with a B.L.B. mask produced no improvement. More careful examination revealed that there was here a left ventricular failure with pulmonary oedema complicating the picture, and I decided to inject pethidine slowly by the intravenous route. The improvement was dramatic after the injection of 50 mg. The muscles relaxed and respiration became slower and deeper, and with more adequate ventilation of the lungs and a high oxygen intake the cyanosis passed off. Treatment was continued on orthodox lines which need not be described in detail, and the patient is making a good recovery.

The lesson I think we should draw from this type of case is that the sequence of events in an acute infection of the respiratory tract in chronic bronchitis is not always clear cut, and in this case I put them as follows. An acute infection of the upper respiratory passages in a patient suffering from chronic bronchitis and emphysema→acute bronchitis→inhalation bronchopneumonia→acute respiratory failure partly due to bronchial spasm but largely due to oedema of the lungs following left ventricular failure.

The management of this type of case obviously needs the greatest care and observation, otherwise a life-saving measure may be missed.—I am, etc.,

Braintree, Essex. BERNARD A. J. MAYO.

Heaf Tuberculin Test

SIR,—As the multiple-puncture tuberculin test is being used more extensively, may I use your *Journal* to advise those using the apparatus that, in order to obtain clearly defined results, it is essential to use sharp needles? The points of the needles supplied are satisfactory for about 2,500 tests, after which they should be sharpened. The old set of needles can be easily replaced by a new set which can be obtained from the manufacturers. The old ones may then be re-sharpened and will be ready to use again.

In carrying out the test, it is important that, in addition to the needles being sharp, they must all penetrate the skin to a uniform depth. It will be appreciated that any bruising due to blunt points or uneven penetration of the needles can make the reading of the tests in persons with low tuberculin sensitivity difficult, as a positive result depends on the presence of at least four points of palpable induration.—I am, etc.,

Cardiff. FREDERICK HEAF.

Testing Limitation of Movement of Spine

SIR,—The sign described by Professor Ian Aird (*Journal*, November 5, p. 1110) for distinguishing functional from organic limitation of movement of the spine will be very useful, particularly if the discrepancy in the degree of flexion in the two positions is large; but if it is moderate or small there are at least three causes besides hysteria and malingering which can make flexion in the sitting position appear greater than when the subject is standing.

(1) The factor of gravity: Ask any patient with so-called "lumbago" to bend down. The sacro-spinales have to pay out while actively contracting to support the weight of the upper part of the body: this causes immediate severe pain with abrupt limitation of flexion. The same patient seated with his legs straight in front of him has virtually no overhang to support, the sacro-spinales are passively stretched and allow further flexion. (2) Concealed knee flexion: Unless great care is exercised to maintain full knee extension when the patient is sitting up and bending forward, a slight degree of knee flexion is easily missed, but it allows a considerable increase in forward trunk flexion. (3) Release of rest stiffness: If a patient has been waiting in the out-patient department some muscle stiffness may have developed and may limit flexion standing, if this is tested first. After changing position—to prone lying and then supine lying and finally sitting—enough stiffness may be released to allow a further degree of flexion. If this is found the patient should again be tested standing, and more flexion will be observed than at the first test; this should be a regular addition to the examination.

I only mention this to avoid injustice being done to patients through the sign being looked for without these points being borne in mind, particularly in cases of examination as to fitness for work or in claims for compensation.—I am, etc.,

Bristol, 8. A. PAUL BODMAN.

Numbering of Fingers

SIR,—It has amused me to follow the discussion about numbering the fingers. To see how it worked, I asked my English wife: "How many fingers do you have?" Of course it was a silly question, but the answer, "Ten," was not in doubt. "Well, where is your first finger?", I proceeded. Out came the index finger, and in turn the little finger as the fourth finger. Now, if she is to possess ten fingers—as the rest of the human race—she obviously must have five on each hand; and when the little finger is the fourth finger, where then is the fifth one? Surely, you don't mean to say that the fifth finger is the thumb, do you?

My conclusion is: you do have five fingers on each hand, and if they are going to be designated 1, 2, 3, etc., you obviously must begin with the thumb. If the thumb is not a finger, what is it, then?—I am, etc.,

Oslo. J. R. LI.

Obituary

A. R. THOMPSON, Ch.M., F.R.C.S.

Mr. A. R. Thompson, consulting surgeon emeritus to the genito-urinary department of Guy's Hospital, died in Nuffield House at Guy's on October 16. He was 79 years of age.

Arthur Ralph Thompson was born on September 3, 1876, and was educated at the Yorkshire College, Leeds, the forerunner of the present university, but then a constituent college of the Victoria University of Manchester, where he graduated M.B., Ch.B. in 1901. He had received his clinical training at Guy's Hospital, and after qualification held a number of resident appointments there. He played as a forward in the Guy's rugger team and also for the Barbarians. In 1902 he was admitted F.R.C.S. and then became resident surgical officer at Guy's, the first holder of this post. For a time also he was house-surgeon at the East London Hospital for Children. Subsequently he became demonstrator of anatomy in Guy's Hospital Medical School and anaesthetist to the hospital. In 1907 he proceeded to the degree of Ch.M., and in the following year he was appointed a Hunterian professor of the Royal College of Surgeons, his subject being "Anatomy of Long Bones Relative to Certain Fractures." Over the course of years he developed a special interest in genito-urinary surgery, and in 1910 he was appointed surgeon in charge of the genito-urinary department at Guy's, a position which he held for twenty-six years. He achieved great eminence in his specialty, being elected president of the Section of Urology of the Royal Society of Medicine in 1931–2.

He was also a vice-president and member of the council of the Anatomical Society of Great Britain and Ireland, a member of the International Association of Urologists, and at one time secretary and vice-president of the Chelsea Clinical Society. From 1912 to 1923 he was an examiner at the Primary examination for the Fellowship of the Royal College of Surgeons. Several of the papers which he published were concerned with the treatment of developmental defects, a field of surgery in which his knowledge of anatomy was particularly useful.

He was the author, with the late Sir Alfred Fripp, of *Human Anatomy for Art Students*, and in recent years he had contributed an interesting series of articles to *Guy's Hospital Gazette* under the general title of "Memories of Guy's." He had also made a study of Homer as a surgical anatomist, and a paper of his on this subject was published in the *Manchester University Medical School Gazette* last year. From 1944 to 1953 he served as a member of a Ministry of Pensions appeals tribunal.

For some forty years the figure of A. R. Thompson —"Rudy," as he was known to the students—was a familiar one at Guy's. His rugged nature and forthright speech came to appeal to staff and patients alike, and many of the latter looked upon him as a friend. The articles he wrote about Guy's as it was fifty or sixty years ago showed how great was his affection for his hospital.

In 1906 he married Miss Florence Wansey, and he is survived by his widow, two sons, and two daughters.

E. W. H. SHENTON, M.R.C.S., L.R.C.P.

We record with regret the death on October 12 of Dr. E. W. H. Shenton, a pioneer radiologist, at the age of 83. He was for many years surgical radiographer at Guy's Hospital, and, later, honorary radiologist at St. Bartholomew's Hospital, Rochester.

Edward Warren Hine Shenton was born on July 12, 1872. He began his medical studies at Guy's Hospital in October, 1893, and from the outset of his student career showed particular interest in the specialty which was to become his life's work. Before he qualified by taking the London Conjoint diploma in 1901 he had been employed as radiographer at Guy's, contemporaneously with A. H. B. Kirkman. The two collaborated to give a practical demonstration of the application of the Roentgen rays in medicine before the Pupils' Physical Society, a report of which was printed in *Guy's Hospital Gazette* of November 4, 1899. Shenton had thus early found his true *métier*, and the great possibilities of roentgenology absorbed his whole attention before and after he qualified. He made several original contributions to his specialty, including a special apparatus for the detection of metallic foreign bodies, and the excellence of his *x*-ray photographs became well known outside Guy's. As a result, he was in popular demand as a demonstrator of the then new science before local medical societies. When the British Medical Association held its Annual Meeting at Exeter in 1907 he acted as one of the honorary secretaries of the Electrical Section. He resigned from the post of senior surgical radiographer at Guy's in 1919 because of the pressure of emergency work, particularly his work as radiologist to the Royal Air Force Central Hospital. For his distinguished services during the first world war he was awarded the Red Cross gold medal.

After the war Shenton developed his consultant practice in Harley Street, and his fame and skill brought him much work. In addition, he was honorary radiographer to St. Peter's Hospital, and for a year he had been medical officer in charge of the electrical department at the Royal London Ophthalmic Hospital. From 1933 to 1950, when he retired, he was honorary radiologist to St. Bartholomew's Hospital, Rochester.

Dr. Shenton's contributions to medical literature were written in a commendably lucid style. All had a bearing on his specialty. His book on *Disease in Bones, its Detection by the X Rays* was published in 1911, and some years later he edited, jointly with A. P. Bertwistle, *A Descriptive Atlas of Visceral Radiograms*. A great lover of music, he composed a number of songs, mostly for children. He not only played the violin well in orchestras and as a soloist, but one of his hobbies was making violins. Soon after the end of the first world war he wrote the libretto and much of the musical score of a revue performed at the Hippodrome, Golders Green, in aid of St. Dunstan's, and in which he played a leading part, for he was also an actor of merit. He was elected an honorary member of the Trinity College of Music, London, in 1944. Another activity was sailing, and he built a 10-ton yacht in the grounds of his home at Golders Green. Shenton had a great zest for life and for work, and he did not give up professional work until his 78th year. He married Miss Phoebe Hollis in 1900, and she collaborated in all his many activities. The sympathy of their many friends will be extended to her in her great loss.

We are indebted to Mr. E. J. GREENWOOD for the following appreciation: It was with great regret that the news of

the death of Dr. E. W. H. Shenton was received in Rochester. He joined us to take charge of the radiological department in 1933, having given up most of his consulting practice in London. He was anxious to show that, although past the usual retiring age for the staff of a teaching hospital, he was still well able to carry out expert work in his specialty. This he certainly did, to the benefit of all his colleagues here, carrying on even under the difficulties of the war years in Kent, and moving to rooms close to St. Bartholomew's Hospital, Rochester, when his services were likely to be called on for air-raid casualties. He finally retired from his active professional work in 1950. His keen co-operation and kindly attitude in giving his expert opinions will always be remembered by those who worked with him. His cheery conversation, whether about his work or about his hobbies, will be recalled by all who knew him. His versatility was remarkable. An expert musician, he had no mean reputation in the musical world both as a violinist and as a composer, the violin on which he played having been constructed by his own hands; he built his own yacht, which unfortunately was finally wrecked near Hastings; and in his later years he was an authority on the growing of roses. His abilities in all these directions were, however, applied with even greater keenness to his profession. His pioneering spirit and enthusiasm made him an outstanding figure in his specialty. He will always be remembered by his colleagues for his character and kindliness.

Professor HANS FINSTERER, who died in Vienna on November 4, aged 78, was born at Weng, Upper Austria, on June 24, 1877, the son of a farmer in humble circumstances. He began the study of medicine at Vienna in 1896, and after graduating in 1902 he became an assistant to Julius Hochenegg at the University surgical clinic. In 1906 he left for a similar post with Viktor Hacker at Graz, returning to Hochenegg in 1909. Both Hacker and Hochenegg had been assistants to Billroth. In 1913 he became Dozent and was appointed lecturer in surgery at the University of Vienna, and in 1920 he was promoted professor extraordinarius. His appointment in 1935 as surgeon-in-chief of the Austrian State hospitals was a recognition of his pre-eminence among the surgeons of his country. Finsterer's name will always be associated with his method of partial gastrectomy for peptic ulcer developed from Hofmeister's modification of the Billroth II operation. He first described this in 1914; four years later he proposed his more radical subtotal gastrectomy. He was a firm advocate of local anaesthesia for abdominal surgery, a method which he first employed in 1912, and which he is said to have used in 8,000 operations subsequently. His important monograph on the subject, *Die Methoden der Lokalanästhesie in der Bauchchirurgie*, appeared in 1923, and was translated into English in the same year. In all he published nearly 300 papers on a great variety of surgical subjects. Finsterer was an honorary fellow of the Royal Society of Medicine, of the Société Nationale de Chirurgie, France, and of the International College of Surgeons, which conferred its highest honour (Master of Surgery) on him in 1949. He was president of the College in 1953.

Dr. R. M. MCCONNELL died in Belfast on October 5 at the age of 54. His whole professional life had been spent in Belfast, where he had a large general practice. Robert Magill McConnell received his medical education at Queen's University, Belfast, graduating M.B., B.Ch. in 1932. He was an excellent doctor, especially gifted as an obstetrician, bringing to his work a shrewd clinical sense, an informed mind, and skilful hands. Integrating all his admirable qualities was a gentle, humorous, and understanding disposition. He was an outstanding personality in Ulster, Irish, and international golf in the inter-war years. He won the Irish amateur open championship in 1927 and the Irish amateur close championship in 1935, being runner-up in the former competition in 1926 and in the latter in 1934. In addition, he was a member of the Irish team from 1924 to 1937. He leaves a widow and two young children, to whom the deepest sympathy goes out from a host of friends.

N. S. D. writes: Dr. R. M. McConnell was laid to rest in the little windswept cemetery of the Presbyterian church in the Castlereagh hills overlooking Belfast, where a few short years before many of his friends had assembled to see him married. Thirty-five years of his life as student and doctor were spent in Belfast, but he was a familiar figure far beyond his native Ulster, and there will be a sense of deep bereavement in the hearts of many people at his passing. A year or so ago he had a serious illness but had made a complete recovery. This spring symptoms of a new illness developed, and, although it appeared to be successfully treated, he had a relapse in June. Distressing in character, painful to a degree, it was borne with great fortitude and courage. Although he spent much of his life in the city he was at heart the true countryman. The countryside, with its sights and sounds and its pursuits, was an unending delight to him. He excelled at everything he put his hand to: at shooting, hunting, or fishing he displayed the same artistry as in his golf. Especially he loved a good horse, and in the handling of one he showed his characteristic understanding and judgment. But it was the companionship these recreations brought him that was of the essence of his enjoyment, and the highlight of the days so spent came in the evenings round the fireside, sharing experiences and living again the events of the day. It was in his love of music that one saw him at his truest and best. From his earliest days he had the greatest interest in music, and throughout his life this was maintained—especially since his marriage was this true, shared as it was by his wife with complete understanding. As memory holds the door wide open there crowd in mind recollections of happy days spent at Punchestown, The Abbey, D'Oyly Carte, John McCormack concerts; of days among the lovely Antrim moors, of the familiar well-loved county of the East Antrim harriers, or of quiet days spent in fishing in his own country around Ballymena. To have known him was a liberal education, to have shared his friendship and companionship a benediction. The memory of these experiences may grow dim with the years, but the memory of his kindness, his gentleness, his sensitive spirit, his love of the simple things of life will always abide.

Dr. N. A. MARTIN died in Sheffield Royal Infirmary on October 26 at the age of 63. Norman Alexander Martin was born at North Shields on October 5, 1892, the eldest son of the late Dr. Angus Martin, and was educated at Berkhamsted School and at the College of Medicine, Newcastle-upon-Tyne, graduating M.B., B.S. from Durham University in 1916. He then entered the R.A.M.C. and served as a captain in Salonika in the first world war, being attached to the 4th Middlesex Regiment. After demobilization he assisted his father at Tynemouth until 1924, when he left to practise on his own account at Southborough, near Tunbridge Wells. Fourteen years later he moved to Bristol, where he practised in Stapleton until 1945. On retirement from general practice Dr. Martin worked as assistant medical officer at the Stoke Park Colony for mental defectives for two years. A further short period in general practice followed, and then, in 1948, he was appointed medical officer at Rampton Hospital, Retford, where he had the medical care of dangerous mental defectives. Later he moved on to other hospitals, but he returned to Rampton for a time. About fifteen months ago his health, which had been failing for some time, began to give cause for anxiety and he was forced to give up work and to rest between periods of treatment in hospital at Sheffield. Dr. Martin was a man of great courage, diligent in his profession and steadfastly conscientious. He had a profound sympathy with his patients and graced his profession with a courtesy which charmed all who came into contact with him. He leaves a widow.

The sudden death of Dr. J. L. MENZIES on October 27 came as a shock to his friends and colleagues in Croydon. He was 68 years of age, and, as he would have wished, died in harness, having only that morning attended his surgeries and visited his patients. John Louis Menzies was born on July 9, 1887, and was educated at Aberdeen University, where he graduated M.B., Ch.B. in 1909. He settled in practice at Croydon in 1914, after having been a house-physician at the Brompton Hospital and on the staff of a sanatorium in Switzerland. He served in the first world war with the R.A.M.C. from 1914 to 1919 and was awarded the Military Cross in 1917. After the war he entered into partnership with the late Dr. A. Rose. In 1920 he proceeded to the M.D., and was appointed to the staff of Croydon General Hospital as a physician, and was later promoted to senior physician, a position which he held until the advent of the National Health Service in 1948. He was a prominent and enthusiastic member of the Croydon hospital management committee, chairman of the Croydon Division of the British Medical Association in 1936–7, and chairman of the local medical committee from 1945 to 1949. In the second world war he served in the R.A.M.C. as assistant director of medical services, North Wales, attaining the rank of lieutenant-colonel. Dr. Menzies was an enthusiastic cricketer. In his early days he captained the Aberdeen University team and played for Aberdeen County. He was also a keen follower of tennis and enjoyed to the full his yearly visit to Wimbledon. Our sympathy is extended to his widow and two sons, one of whom is in the medical profession.—A. A. McA.

Dr. W. J. GRIFFITHS, a general practitioner in Chester for twenty-eight years, and visiting anaesthetist to the Chester Royal Infirmary and Chester City Hospital, died on October 31 at the age of 59. William James Griffiths was born at Bridgend, Glamorganshire, on March 17, 1896, and was educated at Hawarden Grammar School after his family had moved to Chester in 1906. After service in the first world war with the Royal Marines and the Northamptonshire Regiment, into which he was commissioned, he received his medical education at Liverpool University, graduating M.B., Ch.B. in 1924. Following a period as casualty officer at the Royal Southern Hospital, Liverpool, and experience as an assistant in general practice at Gillingham and in Bedfordshire, he returned to Chester in 1926 to take over a single-handed practice. In 1927 he was appointed hon. anaesthetist to the Chester Royal Infirmary, and in 1938 visiting anaesthetist to the Chester City Hospital, appointments which he held until his death. He built up a large general practice in the Hoole and Newton districts of Chester, and it was only after the second world war that he took a first and then a second partner into the practice. In addition to his busy general practice and his work as an anaesthetist, of which he was very fond, he was very active in first-aid work, being appointed a serving Brother of the Order of St. John in 1951 and remaining until his death the medical officer of the Chester division of the British Red Cross Society. He was prominent in masonic circles, served as a Liberal on the Chester City Council from 1947 to 1953, and was a member of the Chester and District and Barrowmore Hospital Management Committees and of the Chester Executive Council. In 1953 he was president of the Chester and North Wales Medical Society. As a result of his sympathetic approach to his patients, his kindness and geniality, he became a very popular and much-loved general practitioner. His Welsh Nonconformist upbringing moved him to take a firm stand on moral principles, to assist his less fortunate fellow citizens in distress, and to righteous indignation at social wrongs and injustices. He took great pride in his city of adoption and was well versed in its history and traditions, but it was the Royal Infirmary, of all its institutions, that he was most proud of. His many friends in so many different circles and walks of life will greatly miss his spontaneous humour and unobtrusive generosity. The long illness which terminated in his sudden death was most courageously borne. He is survived by his widow and young daughter. —T. Ll. H.

Medical Notes in Parliament

Death Penalty Decision

The Government have at length rejected the principal proposals of the Royal Commission on Capital Punishment.

Major G. LLOYD-GEORGE, Home Secretary, stated in a Parliamentary reply on November 10 that the Government had given further consideration to the Commission's report in the light of the debate on February 10. The Commission's recommendations might be divided into three main groups. The first consisted of the major recommendations that the age limit below which the sentence of death may not be imposed should be raised from 18 to 21; that in all other cases the jury should be given discretion to decide whether there were such extenuating circumstances as to justify substituting the sentence of imprisonment for life for the sentence of death; and that the test of criminal responsibility laid down (in England and Wales) by the M'Naghten Rules should be abrogated. The Government, after full consideration, did not feel able to accept any of these three recommendations. The second group consisted of a number of other less important recommendations which could not be implemented without legislation. The Government did not see any prospect of legislation on this matter in the near future, and proposed to defer a decision on these recommendations until an opportunity for legislation could be found. The third group consisted of recommendations to which effect could be given administratively. These had in the main been accepted, and had been, or were being, put into effect. He had, in particular, authorized the Prison Commissioners to proceed with the plans for a special institution for the detention and treatment of psychopaths and other prisoners who are mentally abnormal; and arrangements were now in force whereby persons charged with murder were seen by a psychiatrist from outside the prison service, as well as by a doctor or doctors from within that service, in any case where the prisoner's mental state was in doubt.

Effects of Radiation

The quest for information about the possible genetic and other effects of nuclear radiation, in which the Medical Research Council are conducting a number of investigations, continues unabated in the Commons. Among the items that emerged from Ministerial replies on November 8 were the statements by Mr. J. R. BEVINS, Parliamentary Secretary to the Ministry of Works, that the report of the committee appointed by the Council—which will include a review of existing knowledge—is unlikely to be completed before the spring; and that the Minister of Health hopes to issue in a few months' time a code of practice for the protection of hospital workers from the effects of radiation. Mr. ROY MASON (Barnsley, Lab.) wanted to know to what extent at Harwell, Sellafield, and other active atomic power stations the full permitted dose of radiation was still regarded as safe. Mr. N. BIRCH (Minister of Works) replied that the United Kingdom Atomic Energy Authority, in deciding the maximum permissible level of radiation for their staff, followed the recommendations of the International Commission on Radiological Protection, which were designed to ensure that workers exposed to radiation would not suffer in health. The precautions taken at Harwell and Sellafield in fact reduced the average radiation exposure of employees at those establishments to considerably less than one-tenth of the maximum permissible level.

Mr. MASON also asked which areas of the country the Medical Research Council had in mind for making a study on populations who were subject to varying degrees of natural radioactivity. Mr. BEVINS stated that he was informed by the Council that discussions on a possible

study of populations subject to varying degrees of natural radioactivity were still at an early stage. The Council were therefore not yet in a position to say which areas of the country might be selected.

Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) asked the Under-Secretary of State for Air what consideration had been given to the effect of cosmic rays on personnel flying at high altitudes; and what research had been made on this problem. Mr. GEORGE WARD replied on November 9 that the R.A.F. medical authorities had been watching this problem in the light of information received from a number of sources, including data from instrument-carrying balloons, and they were satisfied that cosmic rays presented no hazard to aircrew flying on Royal Air Force operations.

Disciplinary Procedure

Mr. ALBERT ROBERTS (Normanton, Lab.) asked the Minister of Health if he could investigate the operation of the Health Service Act Disciplinary Procedure in relation to the services administered by the medical executive council, with a view to amending the composition of the appeal panel, in view of the fact that this panel comprised persons appointed by the Minister and that the further appeal from the panel was to the Minister himself. Mr. IAIN MACLEOD stated on November 8 that under arrangements which went back in principle to 1913, and which appeared to have worked satisfactorily in the interests of both patients and doctors, the responsibility for deciding appeals from the decisions of executive councils on complaints against practitioners taking part in the general medical services under the Health Service rested with him and not with a panel. The persons taking oral hearings did so on his behalf.

Points From Scotland

Mr. W. HAMILTON (West Fife, Lab.) asked the Secretary of State for Scotland on November 8 what steps he intended to take to extend the provision of geriatric units throughout the hospital service in Scotland. Mr. J. STUART said that this was a problem to which regional hospital boards were giving the closest attention. Special geriatric units had been developed in some areas, and elsewhere additional specialist facilities had been provided. Work was in progress or about to start very soon on a number of schemes for improvement of existing facilities.

Miss HERBISON (Lanarkshire, North, Lab.) asked how many hospitals had industrial chest units; and if the Secretary of State would encourage hospital boards in areas with a coalfield to establish an industrial chest unit where this had not been done. Mr. STUART told her that the only specific unit of this kind was that at Bangour Hospital, but facilities for diagnosis and treatment were provided by the chest units generally. Any question of special provision on a wider scale was a matter for the regional hospital boards, and the assessment of priorities must be left to them in the light of medical opinion and their knowledge of local needs and circumstances.

Mr. STUART informed Mr. T. HUBBARD (Kirkcaldy, Lab.) that there were 1,812 deaths from lung cancer in Scotland in 1954, and 1,311 in the first three quarters of this year. He also stated that there were 6,470 deaths from coronary thrombosis during the first three quarters of this year, and 6,320 for the corresponding period in 1954. Mr. HUBBARD pressed him to introduce a voluntary notification scheme by local authorities. Mr. STUART said he was advised that merely to compile statistics would not necessarily be very helpful. There were schemes operating in Fife and Kilmarnock. He would consider whether that should be carried further, if medical opinion thought it desirable.

Swiss Sanatoria Treatment

Mr. IAIN MACLEOD said in answer to Mr. GEORGE JEGER (Goole, Lab.) on November 7 that 71 applications by or for tuberculous patients for treatment in Swiss sanatoria from March, 1953, to September, 1955, had to be refused by the responsible consultants as medically unsuitable or too young to be sent. The Swiss scheme cost about £100,000 a year, which had to be found in foreign currency. The cost of treating an equivalent number of patients in sanatoria in this country would be about £75,000.

Hospital Farms

Mr. TUDOR WATKINS (Brecon and Radnor, Lab.) asked the Minister of Health what had been the result of the special committee set up in each regional area which inquired into the farming activities of hospitals; how many hospital farms he had agreed to close; and how many of these were mental and tuberculosis hospitals in each area. Mr. MACLEOD stated on November 7 that reports had been received from regional hospital boards on 207 hospital farms. Decisions had been reached on 112 of these, and discussions were still taking place on the remainder. The decisions reached so far provided for the disposal of land as follows: To be sold, 5,248 acres; to be leased, 3,708 acres; farmland at present leased to be surrendered, 5,618 acres; total 14,574 acres. In 14 cases these decisions involved the complete abandonment of farming activities. Nine of the hospitals involved were mental hospitals, four tuberculosis hospitals, and one a general hospital.

Antioxidants in Food

Sir JOHN CROWDER (Finchley, Con.), on November 10, asked the Minister of Agriculture, Fisheries, and Food which of the recommendations of the committee that considered the use of antioxidants in foods he proposed to implement. Mr. HEATHCOAT AMORY told him that, as the representations made to the department regarding the recommendations raised new issues, including some of a technical nature, they had been referred to the committee for consideration. He was awaiting further advice from the committee on these matters.

Medico-Legal

DOCTOR'S APPEAL TO PRIVY COUNCIL FAILS

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

In November, 1954, Dr. R. T. N. Simpson pleaded guilty at Chelmsford Assizes to charges of indecently assaulting in an unnatural manner certain women patients who had consulted him professionally. On May 26, 1955, the Medical Disciplinary Committee found him guilty from the same facts of infamous conduct in a professional respect, and ordered his name to be erased from the *Register*.[1] At the hearing before the Committee his counsel stated that, though he was not necessarily within the M'Naghten Rules, the doctor had been suffering from a defect of reason of a schizoid nature which made him think that the action which he took was in fact medical treatment in the bona fide interests of his patients, and that fact was accepted by the Judge.

Dr. Simpson appealed under the Medical Act, 1950, against this finding and order. On November 8, 1955, Viscount Simonds delivered the judgment of the Privy Council dismissing the appeal.[2] He said that the appeal board had no reason to suppose that the Committee did not give proper consideration to Dr. Simpson's mental condition, which was brought specially to their notice. Nor could the board understand, accepting the long-familiar test of infamous conduct from Allinson's case as conduct "which would reasonably be regarded as disgraceful and dishonourable by his professional brethren of good repute and competency," how the Committee could have come to any other conclusion. The epithets "disgraceful" and "dishonourable" were scarcely adequate to describe the appellant's acts, and they did not the less deserve the description even if it was assumed that he thought that they would be beneficial to his patients. The Medical Acts were designed at the same time to protect the public and to maintain the high professional and ethical standard of an honourable

[1] *British Medical Journal Supplement*, June 11, 1955, p. 285.
[2] *The Times*, November 8, 1955.

calling. If a practitioner, having committed the grave offences of which the appellant had been guilty, could on such a plea successfully resist the charge of infamous conduct and erasure from the *Register*, the public would lack proper protection and the honour of the profession might be endangered. Counsel for the appellant had urged that the standard of conduct, infamous, disgraceful, or dishonourable, was to be judged by the mental condition of the practitioner. It was not necessary to determine whether there might be circumstances in which weight should be given to such consideration, but upon such evidence as the Committee had before them in this case as to the appellant's mental condition and the nature of his offences the board was clearly of opinion that the Committee had come to a proper conclusion.

The appellant was ordered to pay the costs of the appeal, which was the second to be brought to the Privy Council under the Medical Act, 1950.

Vital Statistics

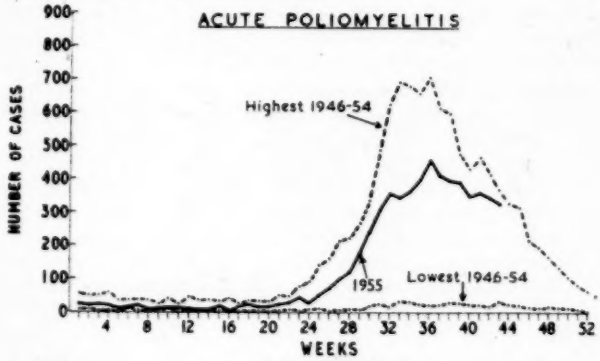
Poliomyelitis

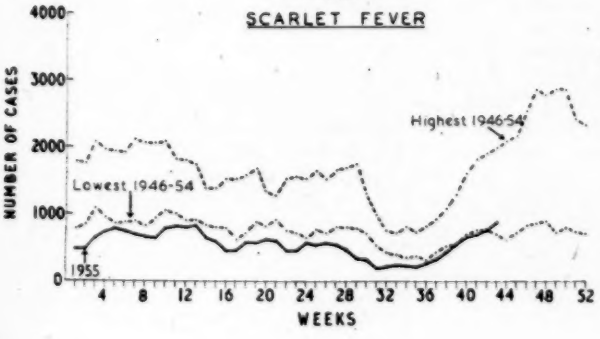
In the week ending November 5 the total number of cases of acute poliomyelitis in England and Wales decreased by 70, paralytic and non-paralytic each being 35 fewer than in the previous week. The figures for the week (with those for the previous week in parentheses) were: paralytic 154 (189); non-paralytic 105 (140); total 259 (329). Notifications from the beginning of the year up to November 5 numbered 6,289, as compared with 8,270 in 1947 and 7,763 in 1950. The incidence of the disease decreased in all regions of England and Wales. 9 deaths were reported.

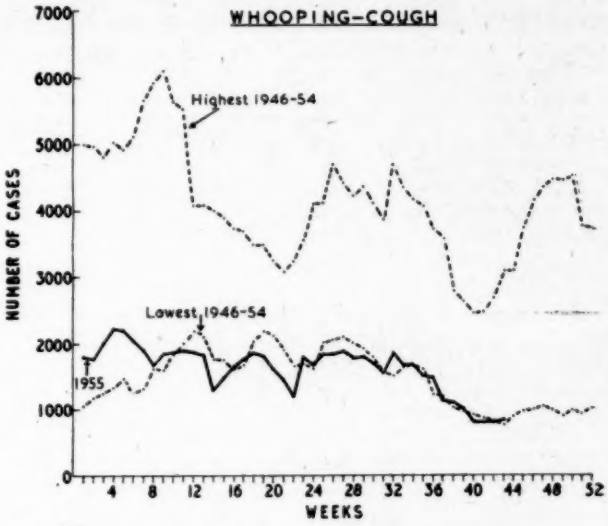
In Scotland 21 cases were notified, 6 fewer than in the previous week.

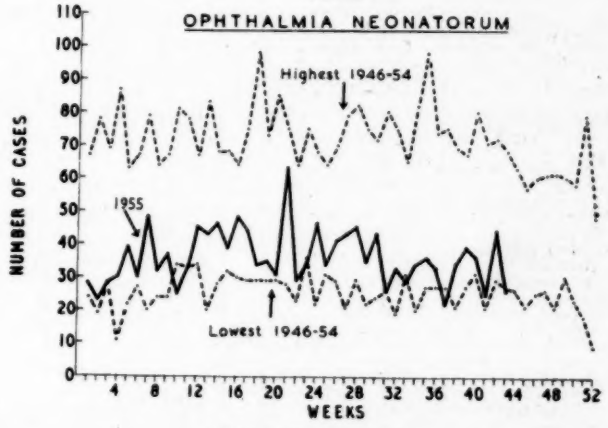
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1946–54 are shown thus ------, the figures for 1955 thus ———. Except for the curves showing notifications in 1955, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

The only variations of note in the notifications of infectious diseases during the week ending October 29 in England and Wales were increases of 185 for measles, from 2,116 to 2,301, and 121 for scarlet fever, from 767 to 888.

The largest rises in the incidence of measles were 99 in Glamorganshire, from 299 to 398, 67 in Devonshire, from 175 to 242, and 65 in Buckinghamshire, from 22 to 87; the largest fall was 47 in Sussex, from 83 to 36. The only large fluctuation in the notifications of scarlet fever was an increase of 42 in Yorkshire West Riding, from 121 to 163. The number of notifications of whooping-cough was 833, an increase of 16 on the total of the preceding week. The largest variations in the returns were an increase of 34 in London, from 38 to 72, and a decrease of 28 in Warwickshire, from 66 to 38. 11 cases of diphtheria were notified, being 2 fewer than in the preceding week. Two cases were notified in three areas, Lancashire, Liverpool C.B. and Manchester C.B., and Staffordshire, Coseley U.D.

A decrease of 49, from 523 to 474, was recorded in the number of notifications of dysentery. The largest returns were Lancashire 94 (Liverpool C.B. 32, Oldham C.B. 13, Ashton-under-Lyne M.B. 10), Yorkshire West Riding 63 (Huddersfield C.B. 19, Todmorden M.B. 10), London 44 (scattered over 18 boroughs), Warwickshire 41 (Meriden R.D. 21, Atherstone R.D. 11), Staffordshire 27 (Newcastle-under-Lyme M.B. 19), Leicestershire 27 (Leicester C.B. 14, Hinckley U.D. 12), and Caernarvonshire 21 (Llandudno U.D. 16).

Week Ending November 5

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 786, whooping-cough 948, diphtheria 5, measles 2,327, acute pneumonia 368, acute poliomyelitis 259, dysentery 482, paratyphoid fever 11, and typhoid fever 5.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 29** (No. 43) and corresponding week 1954.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire	Eire	Eng. & Wales	Lond.	Scot.	N. Ire	Eire
Diphtheria	11	0	6	2		8	1	6	0	
Dysentery	474	44	175	6	2	424	38	204	5	6
Encephalitis, acute	5	0		0		1	0		0	
Enteric fever:										
Typhoid	0	0	0	0		6	0	1	1	
Paratyphoid	12	0	1	0		16	1	2(B)	0	
Food-poisoning	288	46		0		253	55		2	
Infective enteritis or diarrhoea under 2 years				18	38				12	10
Measles*	2,301	33	49	21	65	3,806	254	514	123	124
Meningococcal infection	23	3	12	1		28	2	6	2	
Ophthalmia neonatorum	26	0	10	0		39	4	4	0	
Pneumonia†	329	26	147	4		368	24	141	1	2
Poliomyelitis, acute:										
Paralytic	189	20	27	5	1	40	3	30	1	4
Non-paralytic	140	25				30	4			
Puerperal fever§	237	38	9	0		238	51	12	2	
Scarlet fever	888	53	98	45	23	694	49	128	30	29
Tuberculosis:										
Respiratory	633	93	123	20		784	99	141	12	
Non-respiratory	79	5	15	7		112	13	18	9	
Whooping-cough	833	72	90	65	85	1,692	90	146	9	23

DEATHS in Great Towns	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	1	0	0	0		1	0	0	0	
Infective enteritis or diarrhoea under 2 years	6	0	0	0	2	4	0	1	0	1
Influenza	8	1	0	0	0	9	2	1	0	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	214	32	14	9	3	157	20	16	11	6
Poliomyelitis, acute	11	0			0	2	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	58	8	12	2	2	75	9	4	1	6
Non-respiratory		1	2	1	0		0	6	0	0
Whooping-cough	3	0		0	0	1	0	0	0	0
Deaths 0–1 year	195	27	13	6	10	180	27	22	5	16
Deaths (excluding stillbirths)	4,957	741	533	87	119	4,788	696	491	121	140
LIVE BIRTHS	7,210	1137	858	207	312	7,238	1151	840	204	353
STILLBIRTHS	145	19	23			194	17	20		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Provincial Meeting of the Royal College of Surgeons.—The first provincial meeting of fellows and members of the Royal College of Surgeons of England is to be held in Manchester on December 10. Designed to appeal to general practitioners and hospital officers as well as surgical consultants, the scientific sessions consist of clinical demonstrations in the morning at the Royal Infirmary and a symposium in the afternoon on malignant disease, at which the speakers will be Professor GEOFFREY HADFIELD, Professor IAN AIRD, Sir STANFORD CADE, and Dr. DOUGLAS FRENCH. The annual meeting of fellows and members of the College will be held at 4.30 p.m. In the evening there will be a dinner at Manchester University. Further details are given in our advertisement columns at page 60. As this is a new venture on the part of the College, the council is particularly anxious that the meeting should be well attended. A programme may be obtained from the Secretary, Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2.

Society of Medical Officers of Health.—The Minister of Health, Mr. IAIN MACLEOD, proposed the toast to the Society of Medical Officers of Health at the annual dinner of the Society on November 10. Now that the immediate difficulties of establishing the National Health Service had dropped behind, he hoped that the Service was entering a new era with the emphasis on preventive medicine. He wanted to see a close link between the medical officer of health and the general practitioner, so he was especially delighted to see at the dinner a very distinguished representative of general practice, Dr. WILLIAM PICKLES. The Minister paid a particular tribute to the members of the Society's dental group, who, greatly to their credit, had remained in the public health service when temptations to leave were many, particularly at the start of the National Health Service. Dr. CHARLES F. WHITE, president of the Society, replying to the toast, remarked that medical officers of health were getting over the severe fits of depression which had overtaken them a few years ago. In fact, they were now beginning to have big ideas, as the Society's pamphlet, *Functions of the Medical Officer of Health*, showed. Dr. White thought that after the present centenary year the Society would have to change its name. It was not just a society of medical officers, but one which was glad to embrace all members of the medical and allied professions whose professional interest was preventive medicine. The health of the guests was proposed by Dr. R. H. PARRY, and Sir RUSSELL BRAIN, P.R.C.P., replied.

Chiropody for Old People.—The National Corporation for the Care of Old People has allocated a sum of £60,000 to be spent over the next three years in helping voluntary committees to provide facilities for a chiropody service for old people. This move has the support of the Society of Chiropodists and the Joint Council of Chiropodists, both of which are advising their members to operate in the service at minimum fees. Applications for grants should be addressed to the Secretary, National Corporation for the Care of Old People, Nuffield Lodge, Regent's Park, London, N.W.1.

London Medical Exhibition.—The London Medical Exhibition was held from Monday to Friday of this week in the New Hall of the Royal Horticultural Society, Westminster. The display of pharmaceutical and food products, surgical instruments, hospital equipment, and every kind of accessory and convenience for medical and nursing practice seemed to be larger than ever and even more attractively set out. The number of exhibitors was 120. A feature of the exhibition was the projection of a number of medical films sponsored by various firms. Sir CHARLES DODDS, F.R.S., at a brief opening ceremony, said that a veritable revolution in therapeutics had taken place within the last few years. It was astonishing to recall that antibiotics had been generally available only for some fifteen years, and it

was time to study the changes they had brought about in medicine. Some diseases had been so nearly eliminated that in America several specialist journals had had to cease publication. The conquest of some of the old killing diseases had opened up great possibilities in wider fields.

Royal Medals.—The Queen has approved the award of the Royal Society's two Royal medals for the current year to Sir ALEXANDER TODD, F.R.S., and Professor V. B. WIGGLESWORTH, F.R.S. Sir Alexander Todd is professor of organic chemistry at Cambridge. His recent work on the structure of vitamin B_{12} was the subject of an annotation in this *Journal* on September 3 (p. 610). Professor Wigglesworth, who is a medical man, is a distinguished entomologist. He is Quick professor of biology at Cambridge and director of the Agricultural Research Council's unit of insect physiology.

Postgraduate Travelling Fellowships.—The British Postgraduate Medical Federation (University of London) is prepared to offer a limited number of postgraduate travelling fellowships, tenable for one year, to registered medical and dental practitioners training as specialists in one of the preclinical or clinical branches of medicine, surgery, or dentistry. Further information will be found in our advertisement columns (p. 60).

Fluoridation of Water Supplies.—The following statement has been issued by the Ministry of Health: Before authorizing the four demonstrations of the fluoridation of water supplies which are being arranged in England and Wales, the Minister of Health made a close study of the medical research on the subject which had been carried out in America, and satisfied himself that there was every justification for the demonstrations. He thought it right to give the Standing Medical Advisory Committee an opportunity of putting their own views on record, and has now been advised by the committee that "despite many years of observation and investigation there is no scientific or medical evidence at present available suggesting that there is any risk in drinking water containing added fluoride in the concentration of one part per million."

Committee of Privy Council for Medical Research.—By an Order in Council dated October 28 the Minister of Labour and National Service becomes an additional member of the Committee of Privy Council for Medical Research. This is the Ministerial committee to which the Medical Research Council is responsible. The committee consists of the Lord President (chairman), the Minister of Health, the Secretaries of State for Scotland, the Home Department, Commonwealth Relations, and the Colonies, and now, in addition, the Minister of Labour and National Service. The secretary of the Medical Research Council acts as secretary to this committee. The change in the committee's constitution reflects the increasingly important part that the Medical Research Council is playing in the field of industrial health.

Royal Faculty of Physicians and Surgeons of Glasgow.—At the annual meeting on November 7, the following office-bearers were elected for the ensuing year: President, Professor STANLEY GRAHAM; Visitor, Professor STANLEY ALSTEAD; Hon. Secretary, Dr. A. H. IMRIE; Hon. Treasurer, Dr. J. A. W. MCCLUSKIE; Hon. Librarian, Dr. A. L. GOODALL; Representative on the G.M.C., Dr. ANDREW ALLISON; Councillors, Professor D. F. CAPPELL, Dr. D. MCKAY HART, Mr. ARTHUR JACOBS, Dr. SAMUEL LAZARUS, Dr. W. FERGUSON MACKENZIE, Professor W. ARTHUR MACKEY, Dr. HECTOR R. MACLENNAN, Mr. D. C. MILN, and Dr. GAVIN B. SHAW.

Bequest for Birmingham Medical School.—Dr. STANLEY BARNES, formerly dean of the Faculty of Medicine at Birmingham, who died on August 11, has left the residue of his estate to Birmingham University for the completion of the medical school. The bequest is valued at about £60,000.

Director-General, Army Medical Services.—The QUEEN has approved the appointment of Major-General W. A. D. DRUMMOND as D.G.A.M.S. from April, 1956, in succession to Lieutenant-General Sir FREDERICK HARRIS. Major-General Drummond was born in South Africa in 1901, and educated at Capetown and St. Andrew's University, where he qualified in 1924. He joined the R.A.M.C. the next year, and after regimental service specialized in otolaryngology. During the second world war he served in the Middle East, Persia, and Italy, and from 1946 to 1951 was adviser to the Army in otolaryngology, being stationed at Millbank. In 1951 he became A.D.M.S. Malaya, in 1953 D.M.S. Middle East Land Forces, and in 1954 he was appointed Deputy Director-General.

London University.—Dr. S. W. HINDS, lecturer in child health and social medicine at Bristol University, has been appointed to the University readership in public health tenable at the London School of Hygiene and Tropical Medicine. The title of professor of biology in the University of London has been conferred on Mr. G. E. H. FOXON in respect of his post at Guy's Hospital Medical School.

New Psychological Journal.—The first issue of the *Journal of Analytical Psychology*, dedicated to Professor C. G. JUNG, appeared on October 31. The journal is sponsored by the Society of Analytical Psychology and edited by Dr. MICHAEL FORDHAM. For the time being each volume will consist of two issues (price 12s. 6d. each). The publishers are Tavistock Publications Ltd., 2, Beaumont Street, London, W.1, to whom inquiries should be made. The first number contains articles on "Boar-sacrifice," "Archetypal Themes in Depression," "The Function of Counter-transference," "Loathsome Women," and "The Father Archetype in Feminine Psychology."

Schizophrenic Art.—An exhibition of drawings and paintings by patients with schizophrenia will remain open at the Institute of Contemporary Arts, 17, Dover Street, London, W.1, until December 3. It illustrates the impact of an acute schizophrenic episode on the form and content of the artist's work, the dream-like quality of schizophrenic imagery, schizophrenic stylization, and the characteristic use of written material in the pictures. Perhaps the most instructive exhibit is the series of six paintings by a once-celebrated cat-painter, which shows the change during an acute episode from naturalism to a remarkable heraldic stylization.

£1,000 Award.—The British Diabetic Association announces that an offer of £1,000 has been made for the discovery of "a cure or control" of the Kimmelstiel–Wilson lesion (intercapillary glomerulosclerosis), one of the renal complications of diabetes (see *British Medical Journal*, 1951, 1, 935). Details of the conditions attached to the award may be obtained from the British Diabetic Association, 152, Harley Street, London, W.1.

Dr. W. H. H. Merivale has been appointed director of the department of clinical pathology at Guy's Hospital in succession to Dr. F. A. KNOTT.

Sir Macfarlane Burnet, F.R.S., the virologist, director of the Walter and Eliza Hall Research Institute, Melbourne, is on a two-months visit to Ceylon and India under the auspices of the Colombo Plan.

Dr. T. B. Davie, Principal and Vice-Chancellor of Capetown University, and formerly Professor of Pathology and Dean of the Faculty of Medicine at Liverpool University, is to receive the honorary degree of Doctor of Laws of Liverpool University at a special congregation on November 30.

Mr. A. T. Glenny, F.R.S., who is noted for his work on diphtheria immunization, has been awarded the annual Addingham Medal by the Leeds Faculty of Medicine. The medal, founded in 1933 by a Leeds architect, is for the person "who has made the most valuable discovery for relieving pain and suffering in humanity."

Dr. Elspeth M. Warwick, deputy M.O.H., Nottingham, has gone to Nigeria on behalf of the World Health Organization to advise on the establishment of maternal and child health services there.

COMING EVENTS

London Medical Orchestra.—Concert in aid of the Infantile Paralysis Fellowship at B.M.A. House, Tavistock Square, London, W.C.1, at 8 p.m. on December 10. Tickets at the door.

Hospitals' Symphony Orchestra.—Concert at the Royal College of Surgeons, Lincoln's Inn Fields, at 7.30 p.m., on November 26. Tickets (10s., 7s. 6d., 5s., 3s. 6d.) from Miss M. A. WHIPP, Almoners' Department, St. Thomas's Hospital, London, S.E.1.

NEW ISSUES

Archives of Disease in Childhood.—The new issue (Vol. 30, No. 153) is now available. The contents include:

CALCIUM METABOLISM IN IDIOPATHIC HYPERCALCAEMIA OF INFANCY WITH FAILURE TO THRIVE. R. E. Bonham Carter, C. E. Dent, Dorothy I. Fowler, and Christine M. Harper.
PROTEIN CATABOLISM AND RENAL FUNCTION IN THE FIRST TWO DAYS OF LIFE IN PREMATURE INFANTS AND MULTIPLE BIRTHS. R. A. McCance and E. M. Widdowson.
PROGERIA AND ATHEROSCLEROSIS. A. J. Keay, M. F. Oliver, and G. S. Boyd.
A FOLLOW-UP STUDY OF 110 PATIENTS TREATED FOR PURULENT MENINGITIS. Elly M. Desmit.
ORAL FACTORS IN ACCIDENTAL POISONING. J. O. Craig.
THE EFFECT OF PANCREATIN THERAPY ON FAT ABSORPTION AND NITROGEN RETENTION IN CHILDREN WITH FIBROCYSTIC DISEASE OF THE PANCREAS. Ruth Harris, A. P. Norman, and W. W. Payne.
NON-PANCREATIC LIPASE IN CHILDREN WITH PANCREATIC FIBROSIS. Constance A. C. Ross and H. G. Sammons.
AN ANTHROPOMETRIC STUDY OF EDINBURGH SCHOOLCHILDREN. PART II: COMMENTS ON RESULTS. Lilli Stein.
THE VALUE OF SPLENECTOMY IN FANCONI'S ANAEMIA. R. C. Francis, R. A. Moir, and P. N. Swift.
THE VITAL CAPACITY OF CHILDREN. H. Everley Jones.
PREMATURE LOSS OF DECIDUOUS TEETH. R. S. Illingworth and J. H. Gardiner.
EPILEPSY DUE TO BIRTH INJURY IN ONE OF IDENTICAL TWINS. S. D. V. Weller and R. M. Norman.
PULMONARY CYSTS FOLLOWING INGESTION OF HOUSEHOLD PARAFFIN. Andrew Skarbek.
CONGENITAL THYROTOXICOSIS, HEPATOSPLENOMEGALY, AND JAUNDICE IN TWO INFANTS OF EXOPHTHALMIC MOTHERS. M. O. Skelton and B. Gans.
SUPPURATIVE PERICARDITIS DUE TO A PENICILLIN- AND STREPTOMYCIN-RESISTANT STAPHYLOCOCCUS. W. H. P. Cant, K. D. Roberts, and K. B. Rogers.
ACUTE BENIGN PERICARDITIS IN INFANCY. W. P. Sweetnam and C. G. W. Sykes.
CHRONIC REGIONAL ENTERITIS IN CHILDHOOD. T. G. Maddison and I. Hyde.
RETICULUM-CELL SARCOMA IN INFANCY. Wallace M. Dennison.
PARTIAL ABSENCE OF THE TRACHEA WITH LIVE BIRTH. A. T. Sandison.

Issued six times a year; annual subscription £3 3s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Saturday, November 19

KENT PAEDIATRIC AND CHILD HEALTH SOCIETY.—At Royal Star Hotel, Maidstone, 3 p.m., Dr. A. J. Dalzell-Ward: Child Care in Turkey—a review of personal experience in Turkey.

Monday, November 21

HUNTERIAN SOCIETY.—At Apothecaries Hall, 8.30 p.m., discussion: Capital Punishment: Remains a Necessity in Modern Society. Proposed by Lord Justice Denning and Dr. W. L. Neustatter. Opposed by the Rt. Hon. Chuter Ede and Dr. Desmond Curran.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, 5.30 p.m., Dr. J. W. Trevan, F.R.S.: Pharmacology of Respiratory Regulation.

Tuesday, November 22

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. R. D. Harkness: Metabolism of Collagen.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. C. Wells: The Sebum.
●INSTITUTE OF NEUROLOGY.—5.30 p.m., Dr. J. H. Paterson: Pain in Relation to Lower Limbs.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—12 noon, Professor J. Young: Maternal Mortality in Great Britain.
MANCHESTER MEDICAL SOCIETY.—At Manchester University, 4.30 p.m., University Lecture on the History of Medicine by Dr. D. A. K. Black: Patients and Doctors in Classical Times.
●OXFORD UNIVERSITY MEDICAL SOCIETY.—At George Restaurant, 8.15 p.m., annual dinner. Speakers, Sir Arthur Porritt, Professor G. W. Pickering, and Sir William MacArthur.
ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Brigadier Ian Fraser: Some Problems of the Small Intestine.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Mr. R. B. K. Rickford: Clinical Significance of Retroversion of the Uterus and Treatment (if any).
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. C. C. Edwards: Neurological demonstration.

Wednesday, November 23

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., symposium: The Temporal Lobe. Speakers, Professor P. C. P. Cloake, Dr. R. W. Tibbetts, and Mr. E. A. Turner.
BRITISH ASSOCIATION OF SPORT AND MEDICINE.—At St. Thomas's Hospital Medical School, 5 p.m., Dr. J. H. Cyriax: Clinical Examination of the Injured Athlete. Manual Treatment or Hydrocortisone.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. D. S. M. Barlow: Carcinoma of the Oesophagus.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. A. R. C. Higham: Enuresis.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. P. M. F. Bishop: Endocrinological Investigations
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Robert Jones Lecture by Professor B. L. McFarland: The Crooked Tree.
ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Mr. A. W. Kay: Modern Trends in Peptic Ulcer Therapy.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. G. J. V. Crosby: General Practice and the Public Health.
ROYAL MEDICAL SOCIETY, EDINBURGH.—8 p.m., clinical meeting.
ST. MARYLEBONE HOSPITAL FOR PSYCHIATRY AND CHILD GUIDANCE.—5.30 p.m., Dr. W. M. McIntyre: Schools of Psychotherapy.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Dr. M. A. Partridge: lecture demonstration in psychiatry.

Thursday, November 24

ASSOCIATION OF MEDICAL RECORDS OFFICERS.—At King George Hospital, Ilford, 6.30 p.m., Tour of Records Department, with explanation of procedures by Miss E. Chrystal.
BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor J. C. McC. Browne: Isotopes in the Study of Problems of Pregnancy.
COLLEGE OF GENERAL PRACTITIONERS.—At Ronkswood Hospital, Worcester, 3.30 p.m., clinical meeting.
HONYMAN GILLESPIE LECTURES.—At University New Buildings, Teviot Place, Edinburgh, 5 p.m., Professor W. A. Mackey: Death following Operation for Mitral Stenosis.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Blood and Bone Marrow in Skin Diseases.
LIVERPOOL MEDICAL INSTITUTION.—8 p.m., pathological meeting.
●LONDON MARRIAGE GUIDANCE COUNCIL.—At National Association for Mental Health, 7 p.m., Dr. P. M. Bloom: Early Psycho-Sexual Problems in Marriage.
LONDON VARICOSE CLINIC.—8.15 p.m., Anniversary Clinical Meeting. Dr. Stanley Rivlin: Approach to the Ulcerated Leg. (Illustrated by films and slides.)
●NUFFIELD ORTHOPAEDIC CENTRE, Wingfield-Morris Orthopaedic Hospital, Oxford, 8.30 p.m., Dr. L. Guttmann: The Initial Treatment of Traumatic Paraplegia.
ROYAL EYE HOSPITAL.—5.15 p.m., Dr. T. H. Whittington: Aspects of Refraction.—7. Eyes and Sight of Young Children.
ROYAL NORTHERN HOSPITAL.—2.45 p.m., Dr. W. E. Clarke: Heart Failure and its Treatment.
ST. ANDREWS UNIVERSITY.—At Physiology Department, Queen's College, Dundee, 5 p.m., Sir Harold D. Gillies: Practice of Plastic Surgery—A General Review.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. D. Curran: postgraduate demonstration in psychiatry.
SURREY INTER-HOSPITAL PSYCHIATRIC ASSOCIATION.—At St. Lawrence's Hospital, Caterham, Surrey, 6.30 p.m., Dr. B. W. Richards: Mental Deficiency Problems Viewed Statistically.
WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At West London Hospital, 8.30 p.m., Dr. T. F. Fox: Russia Revisited.

Friday, November 25

GLASGOW UNIVERSITY MEDICO-CHIRURGICAL SOCIETY.—At Edinburgh, 7.30 p.m., debate with Royal Medical Society. "This House Considers that Sterilization of the Unfit be Enforced."
●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. B. Dowling: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Sir Clement Price Thomas.
MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES.—At 11, Chandos Street, W., 6.45 for 7.30 p.m., Dr. C. S. Nicol: Social Aspects of Gonorrhoea.
MIDDLESEX HOSPITAL MEDICAL SCHOOL.—5.15 p.m., advanced lecture in physiology by Dr. R. L. Riley (Baltimore): Recent Work on the Exchange of Gases Between Alveolar Air and the Blood in Man.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 2 p.m., Mr. H. C. Edwards: Non-specific Granulomata of the Terminal Ileum, Caecum, and Ascending Colon. (2) 4 p.m., Professor A. W. Woodruff: Filarial Infections.
●ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS.—5.30 p.m., William Blair-Bell Memorial Lecture by Mr. A. M. Sutherland: Tuberculosis of the Endometrium.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Crowe.—On October 27, 1955, at St. George's Hospital, London, S.W., to Judith, wife of Dr. Peter Crowe, a son—Philip John.
Evans.—On November 7, 1955, at St. David's Hospital, Bangor, to Dr. Joan Evans (formerly Wilson), and Dr. Emrys Evans, a son.
Green.—On November 9, 1955 at Charing Cross Hospital, London, W.C., to Doreen, wife of Dr. Brian P. Green, a daughter—Lesley Jane.
Sinclair.—On October 6, 1955, to Drs. Olive M. (formerly Russell) and Wilfred Sinclair, of Kota Kota, Nyasaland, a daughter.

DEATHS

Bennett.—On October 15, 1955, at St. Vincent's Clinic, Ladbroke Terrace, London, W., Victoria Evelyn May Bennett, M.B., B.S., D.P.H., formerly of 99, Oakley Street, Chelsea, London, S.W., aged 89.
Calleja.—On October 17, 1955, at a nursing-home, Jersey, C.I., Roger V. P. Calleja, O.B.E., M.D., D.T.M.&H.
Thompson.—On October 16, 1955, at Guy's Hospital, S.E., Arthur Ralph Thompson, Ch.M., F.R.C.S.
Watson.—On October 14, 1955, at Liphook, Hants, Robert Henry Watson, M.D., aged 91.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Wakeful Baby

Q.—*My son, aged 14 months, regularly wakes at 1 a.m. and refuses to go to sleep again unless given a mixture containing 45 min. (2.7 ml.) of syrup of chloral and 4½ gr. (0.29 g.) of potassium bromide. He sits up and plays in his cot. This is wearing out my wife, who is expecting another baby. Is there any harm likely to result from regular and continued use of this hypnotic? During the day the boy rests for 1½ hours in the morning, and is put to bed at 8 p.m. He seems perfectly well in spite of the loss of sleep. What alternative measures are recommended?*

A.—This is a not uncommon problem. It is not abnormal for a baby in his second year to sit up, play, and even sing in the early morning hours. The child is healthy, and the mother should be reassured that there is no cause for anxiety on his account and that his early waking is almost certainly a temporary phase. If the baby shares his parents' room he should be given one of his own at some distance from theirs. His cot must be secure and the room both well ventilated and effectively darkened. He should go to bed with his favourite toys, and adequately clothed to ensure sufficient warmth. If heard to be awake he should not be visited and no attempts should be made to persuade him to lie down. The routine continuous use of sedatives is not desirable. The drug of choice is chloral hydrate (without bromide). It should be given at night only, when the child retires, in a dose of 6 gr. (0.39 g.), increasing to 8 gr. (0.52 g.) if necessary, but not being persisted with for more than seven to ten days.

Functional Efficiency in Bicycle Design

Q.—*What human factors must be taken into consideration in bicycle design so as to combine maximum comfort with efficiency? Is the racing bicyclist, with low handlebars, in the best position for maximum physiological efficiency?*

A.—Very few investigations have been made on the design of bicycles, progress having taken place gradually, mainly by trial and error. However, it is doubtful whether any physiologist could improve the design.[1] What information there is has been obtained from experiments on stationary bicycle ergometers, which, of course, ignore the effort required to maintain balance and to overcome air resistance.

One of the factors that will affect efficiency is the relative position of the seat and pedals. Experiments using a bicycle ergometer have shown that there are two optimum positions. One corresponds closely to the conventional design in which the forces are mainly gravitational. The other with a back-rest and the lower limbs nearly horizontal, in which the forces are produced by a mechanical toggle action between back-rest and pedals,[2] essentially the position adopted in the French "velocar." It may be that this arrangement has certain advantages if the thrust required on the pedals is high, because it has been found in experiments on young men that over 500 lb. (227 kg.) can be exerted by each foot in this position.[3] Also, by allowing a lower centre of gravity to the machine, it might reduce the energy required to keep the balance, and the provision of a seat and back-rest might offer more comfortable support for extended periods "at the wheel." Another factor which might be investigated is the radius of pedal travel in relation to the range and axes of lower limb movements and to the forces developed at different phases. Mechanical considerations that will affect the rider include functional resistance of the bicycle, its centre of gravity, air resistance, and vibration.

It is probable that the position of the racing bicyclist is not the optimum for maximum physiological efficiency, owing to the restriction it imposes on breathing, but any disadvantages are no doubt outweighed by the reduction in air resistance and the increased tension that can be developed in the hip extensors.

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1 Hill, A. V., *Lancet*, 1951, **2**, 947.
2 Hugh-Jones, P., *J. Physiol.*, 1947, **106**, 186.
3 —— Ibid., 1947, **105**, 332.

Anaphylactoid Reactions to Penicillin

Q.—*I have become alarmed by the reported anaphylactoid reaction to penicillin, and I should like to know if it would be advisable to give an antihistamine drug as a routine precaution at the time of each injection or oral dose of penicillin.*

A.—A number of investigators have attempted to reduce anaphylactoid reactions to penicillin by the simultaneous administration of oral and/or parenteral antihistamines. Some reports suggest that a reduction in the incidence of untoward reactions is thus obtained, but even so, as Simon *et al.*[1] point out, the ideal result of no reactions will never be reached. In a controlled study with more than 2,000 courses of penicillin given to University students at Michigan, Matthews *et al.*[2] found no significant difference in the incidence of severe or delayed penicillin reactions between those receiving oral or parenteral antihistamines and the controls. On the evidence at present, the simultaneous administration of any antihistaminic cannot be recommended as a worth-while routine precaution. It is, however, most advisable that the doctor and the nurse should inquire of each patient before giving penicillin whether any untoward reaction has ever occurred after penicillin administration. The precautions recently advised in this *Journal* should, of course, be observed.[3 4]

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1 Simon, S. W., Berman, H. I., and Rosenblum, S. A., *J. Allergy*, 1954, **25**, 395.
2 Mathews, K. P., Hemphill, F. M., Sheldon, J. M., Lovell, R. G., and Forsythe, W. E., ibid., 1955, **26**, 78.
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Cold Extremities

Q.—*How am I to keep my hands and feet warm this winter? I have no chilblains, and in spite of extra warm clothing my periphery is painfully cold at times. Immersing my hands in hot water gives only very transient improvement.*

A.—Undue cooling of the extremities on exposure to cold is a troublesome symptom, and far and away the best treatment is the avoidance of exposure, by living and sleeping in warm rooms and having an efficient car-heater. As the condition is in part due to an over-reactive nervous system, it may be helped by the avoidance of overwork and smoking, relief of anxieties, and adequate sleep and exercise. Drugs which may be tried are thyroid, nicotinic acid, and tolazoline hydrochloride. The last is probably the best for ambulant treatment, and the usual dose is 50 mg. three or four times a day by mouth.

Projection Television

Q.—*I intend installing a projection television set. Have measurements been made on the emission of x rays from the cathode-ray tube of commercial domestic projection television receivers? If so, is adequate screening provided by the manufacturers?*

A.—Measurements on the emission of *x* rays from projection television receivers have been carried out by the National Physical Laboratory. These have shown that with the cathode-ray tube inside the set the screening provided by the manufacturers is such that the emission of *x* rays outside is negligibly small, and that no danger arises to the viewer from this source, even under conditions of long and continuous viewing.

Hirsutism in Female Diabetics

Q.—*Is hirsutism in the female a recognized concomitant of diabetes or complication of heavy insulin dosage? A woman of 24 who has been having large doses of insulin since the age of 11 has marked facial hirsutism which embarrasses her.*

A.—Hirsutism has not been described as a complication of insulin therapy, but is found not infrequently in diabetics of post-menopausal age. A syndrome of this last type has indeed been described by Achard and Thiers.[1] Assuming that the patient described is not suffering from Cushing's syndrome or acromegaly, it would seem probable that the hirsutism and diabetes are coincidental, rather than directly related.

REFERENCE

[1] Achard, C., and Thiers, J., *Bull. Acad. Méd. (Paris)*, 1921, **86**, 51.

Thrombosis During Rauwolfia Therapy

Q.—*An elderly female who has had a mild hypertension (170–180/90 mm. Hg) for probably 20 years has suffered from headaches for much of that time. Of recent years they have become more severe and throbbing in character, and during the past year have been accompanied by an awareness of arterial pulsation, particularly when in bed. In 1953 a retinal haemorrhage occurred in one eye and has left the vision impaired. "Rauwiloid" was prescribed in 1954, as it was considered, following negative investigations, that a functional element contributed to the headaches. Following an initial dose of two tablets daily for a month, a maintenance dose of one tablet daily was continued. This resulted in some relief of headaches and throbbing, the blood pressure fell to 145/70, and the pulse slowed from a previous 90 to 70 per minute. Three months after beginning treatment there was a sudden blurring of vision in the sound eye, but no definite ophthalmoscopic changes were to be seen other than evidence of arteriosclerosis. Nevertheless, a "spot" still persists over this eye. Following this episode, the rauwiloid was discontinued, with the result that symptoms have reverted to their old level of severity, and the blood pressure and pulse have also reverted to former levels. The patient is anxious to try rauwiloid again. Is it likely that this drug was the cause of the second visual incident by promoting thrombosis, and with this history is it considered safe to exhibit a substance which appears to effect a 20-millimetre fall in diastolic pressure in this individual?*

A.—The hypertension from which this old lady suffers is of the pure systolic type so often associated with arteriosclerosis in the elderly. In such patients the risk of thrombosis is ever present. Gross reduction of blood pressure could so diminish the flow through diseased vessels as to favour thrombosis. The moderate reduction of pressure seen with a rauwolfia preparation can hardly be blamed for an additional thrombotic accident. If the patient was definitely more generally comfortable on this preparation it should be started again. There is, moreover, no conclusive evidence that the persistent "spot" has really resulted from a vascular occlusion in the eye or visual areas in the brain.

Pterygium

Q.—*Is pterygium always the result of chronic infection? What treatment is recommended for the fleshy type not yet invading the cornea?*

A.—Pterygium is probably never the result of chronic infection; it is a degenerative condition, primarily of the limbus and cornea, of unknown aetiology, in which, however, long-continued irritation from wind, sand, and so on undoubtedly plays a part. No treatment is required for the fleshy type which has not yet invaded the cornea, unless excision or transplantation and burying is desired for cosmetic purposes.

NOTES AND COMMENTS

Protein and Fat in Diets for Obesity.— Professor JOHN YUDKIN (London, W.8) writes: In your answer to the question concerning diets for obesity ("Any Questions?" October 8, p. 921) you say that there is no advantage gained by giving more than the minimum of fat during weight reduction. Research during the last two or three years has shown that this statement is not correct.[1 2 3] The effects on weight reduction have been compared of giving various diets, equally low in calories, but constructed with different proportions of fat and carbohydrate. It was perhaps not surprising to find that, although the calories were equal, diets containing a higher proportion of fat were much preferred by the obese subjects consuming them. The known high satiety value of fat explains why the subject felt less hungry and altogether more contented during weight reduction. What was surprising, however, was the fact that, on these equal low-calorie diets, weight reduction was appreciably more rapid on the diets with more fat. Thus, there are two advantages to be gained by giving more fat in a reducing diet—the diet is much more acceptable (and consequently more likely to be adhered to) and at the same time it is more effective in weight reduction.

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[2] Brewer, W. D., Cederquist, D. C., Williams, B., Beegle, R. M., Dunsing, D., Kelley, A. L., and Ohlson, M. A., ibid., 1952, **28**, 213.
[3] Kekwick, A., and Pawan, G. L. S., *Arch. Middx Hosp.*, 1953, **3**, 139.

"Calgon" and Hypodermic Syringes.—Mr. G. H. DARLING (chief pharmacist, Bristol Royal Hospital) writes: May I be allowed to comment on the reply given to the query regarding the use of "calgon" in the water in which syringes are boiled ("Any Questions?" October 15, p. 980)? For some time we have been carrying out trials in the wards of this hospital on the use of chemicals to prevent the deposition of hard water fur on bowls and instruments. Calgon and the tetra-sodium salt of E.D.T.A. (ethylenediamine tetra-acetic acid) have both been used, and we have found the latter to be somewhat superior. Unfortunately, in our experience, both these compounds have been found to remove the enamelled graduations from syringes, the speed with which this takes place being related to the concentration and the frequency with which the syringes are boiled. While we are very satisfied with the results when boiling metal instruments, we have had to revert to the use of distilled water for syringes.

Catheterization in General Practice.—Mr. HUGH DONOVAN (Birmingham) writes: I note under the heading "Any Questions?" (October 8, p. 920) advice on the passage of a catheter in a private house. May I make the following comment, as I believe it to be of very great importance indeed? Whenever a hollow instrument is introduced into the bladder and before it is removed, there should always be instilled an ounce or two (30–60 ml.) of an effective antiseptic lotion. I am satisfied that this reduces the chance of infecting the bladder to virtually nil, and if I personally omit to do it my conscience charges me with malpractice. The lotion I use is oxycyanide of mercury, 1 in 6,000. As is well known, this lotion must not be used for bladder lavage because of the danger of mercurial poisoning; 1–2 oz. (30–60 ml.), however, can be used on isolated occasions, because if such a quantity were drunk it would perhaps scarcely poison the patient.

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